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(54) Title: NOVEL GENE DISRUPTIONS, COMPOSITIONS AND METHODS RELATING THERETO

(57) Abstract: The present invention relates to transgenic animals, as well as compositions and methods relating to the characterization of gene function. Specifically, the present invention provides transgenic mice comprising disruptions in PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 genes. Such in vivo studies and characterizations may provide valuable identification and discovery of therapeutics and/or treatments useful in the prevention, amelioration or correction of diseases or dysfunctions associated with gene disruptions such as neurological disorders; cardiovascular, endothelial or angiogenic disorders; eye abnormalities; immunological disorders; oncological disorders; bone metabolic abnormalities or disorders; lipid metabolic disorders; or developmental abnormalities.

NOVEL GENE DISRUPTIONS, COMPOSITIONS AND METHODS RELATING THERETO

FIELD OF THE INVENTION

The present invention relates to compositions, including transgenic and knockout animals and methods of using such compositions for the diagnosis and treatment of diseases or disorders.

BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as

pharmaceutical and diagnostic agents. Receptor immuno-adhesions, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

Given the importance of secreted and membrane-bound proteins in biological and disease processes, *in vivo* studies and characterizations may provide valuable identification and discovery of therapeutics and/or treatments useful in the prevention, amelioration or correction of diseases or dysfunctions. In this regard, genetically engineered mice have proven to be invaluable tools for the functional dissection of biological processes relevant to human disease, including immunology, cancer, neuro-biology, cardiovascular biology, obesity and many others. Gene knockouts can be viewed as modeling the biological mechanism of drug action by presaging the activity of highly specific antagonists *in vivo*. Knockout mice have been shown to model drug activity; phenotypes of mice deficient for specific pharmaceutical target proteins can resemble the human clinical phenotype caused by the corresponding antagonist drug. Gene knockouts enable the discovery of the mechanism of action of the target, the predominant physiological role of the target, and mechanism-based side-effects that might result from inhibition of the target in mammals. Examples of this type include mice deficient in the angiotensin converting enzyme (ACE) [Esther, C.R. et al., Lab. Invest., 74:953-965 (1996)] and cyclooxygenase-1 (COX1) genes [Langenbach, R. et al., Cell, 83:483-492 (1995)]. Conversely, knocking the gene out in the mouse can have an opposite phenotypic effect to that observed in humans after administration of an agonist drug to the corresponding target. Examples include the erythropoietin knockout [Wu, C.S. et al., Cell, 83:59-67 (1996)], in which a consequence of the mutation is deficient red blood cell production, and the GABA(A)-R- β 3 knockout [DeLorey, T.M., J. Neurosci., 18:8505-8514 (1998)], in which the mutant mice show hyperactivity and hyper-responsiveness. Both these phenotypes are opposite to the effects of erythropoietin and benzodiazepine administration in humans. A striking example of a target validated using mouse genetics is the ACC2 gene. Although the human ACC2 gene had been identified several years ago, interest in ACC2 as a target for drug development was stimulated only recently after analysis of ACC2 function using a knockout mouse. ACC2 mutant mice eat more than their wild-type littermates, yet burn more fat and store less fat in their adipocytes, making this enzyme a probable target for chemical antagonism in the treatment of obesity. [Abu-Elheiga, L. et al., Science, 291:2613-2616 (2001)].

In the instant application, mutated gene disruptions have resulted in phenotypic observations related to various disease conditions or dysfunctions including: CNS/neurological disturbances or disorders such as anxiety; eye abnormalities and associated diseases; cardiovascular, endothelial or angiogenic disorders including atherosclerosis; abnormal metabolic disorders including diabetes and dyslipidemias associated with elevated serum triglycerides and cholesterol levels; immunological and inflammatory disorders; oncological disorders; bone metabolic abnormalities or disorders such as arthritis, osteoporosis and osteopetrosis; or a developmental disease such as embryonic lethality.

SUMMARY OF THE INVENTIONA. Embodiments

The invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286,
 5 PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203
 10 or PRO35250 polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid
 15 sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94%
 20 nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122,
 25 PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820,
 30 PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

35 In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid

sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide cDNA as disclosed herein, the coding sequence of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity,

alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides are contemplated.

The invention also provides fragments of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944,

PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody or as antisense oligonucleotide probes. Such nucleic acid fragments usually are or are at least about 10 nucleotides in length, alternatively are or are at least about 15 nucleotides in length, alternatively are or are at least about 20 nucleotides in length, alternatively are or are at least about 30 nucleotides in length, alternatively are or are at least about 40 nucleotides in length, alternatively are or are at least about 50 nucleotides in length, alternatively are or are at least about 60 nucleotides in length, alternatively are or are at least about 70 nucleotides in length, alternatively are or are at least about 80 nucleotides in length, alternatively are or are at least about 90 nucleotides in length, alternatively are or are at least about 100 nucleotides in length, alternatively are or are at least about 110 nucleotides in length, alternatively are or are at least about 120 nucleotides in length, alternatively are or are at least about 130 nucleotides in length, alternatively are or are at least about 140 nucleotides in length, alternatively are or are at least about 150 nucleotides in length, alternatively are or are at least about 160 nucleotides in length, alternatively are or are at least about 170 nucleotides in length, alternatively are or are at least about 180 nucleotides in length, alternatively are or are at least about 190 nucleotides in length, alternatively are or are at least about 200 nucleotides in length, alternatively are or are at least about 250 nucleotides in length, alternatively are or are at least about 300 nucleotides in length, alternatively are or are at least about 350 nucleotides in length, alternatively are or are at least about 400 nucleotides in length, alternatively are or are at least about 450 nucleotides in length, alternatively are or are at least about 500 nucleotides in length, alternatively are or are at least about 600 nucleotides in length, alternatively are or are at least about 700 nucleotides in length, alternatively are or are at least about 800 nucleotides in length, alternatively are or are at least about 900 nucleotides in length and alternatively are or are at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190,

PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO69122, PRO204, PRO214, PRO222,

PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide fragments that comprise a binding site for an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention provides isolated PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity,

alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In one aspect, the invention concerns PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polypeptides which are or are at least about 10 amino acids in length, alternatively are or are at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more. Optionally, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polypeptides will have or have no more than one conservative amino acid substitution as compared to the native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence, alternatively will have or will have no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to the native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence.

In a specific aspect, the invention provides an isolated PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384,

PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide without the N-terminal
 5 signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994,
 10 PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646,
 15 PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and recovering the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,
 20 PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO69122, PRO204, PRO214, PRO222, PRO234,
 25 PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182,
 30 PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO69122, PRO204,
 35 PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926,

PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and recovering the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide from the cell culture.

The invention provides agonists and antagonists of a native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as defined herein. In particular, the agonist or antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody or a small molecule.

The invention provides a method of identifying agonists or antagonists to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide which comprise contacting the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332,

PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Preferably, the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is a native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

The invention provides a composition of matter comprising a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, or an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342,

PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as herein described, or an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

The invention provides the use of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, or an agonist or antagonist thereof as hereinbefore described, or anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944,

anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

The invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

The invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

The invention provides oligonucleotide probes which may be useful for isolating genomic and cDNA nucleotide sequences, measuring or detecting expression of an associated gene or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences. Preferred probe lengths are described above.

The invention also provides a method of identifying a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980,

PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal; and

(c) comparing the measured physiological characteristic with that of a gender matched wild-type animal,

5 wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal. In one aspect, the non-human transgenic animal is a mammal. In another aspect, the mammal is a rodent. In still another aspect, the mammal is a rat or a mouse. In one aspect, the non-human transgenic animal is heterozygous for the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In another aspect, the phenotype exhibited by the non-human transgenic animal as compared with gender matched wild-type littermates is at least one of the following: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

In yet another aspect, the neurological disorder is an increased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is a decreased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is an abnormal circadian rhythm during home-cage activity testing. In yet another aspect, the neurological disorder is an enhanced motor coordination during inverted screen testing. In yet another aspect, the neurological disorder is impaired motor coordination during inverted screen testing. In yet another aspect, the neurological disorder includes depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety, autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder, enhancement of cognitive function, loss of cognitive function associated with but not limited to Alzheimer's disease, stroke, or traumatic injury to the brain, seizures resulting from disease or injury including but not limited to epilepsy, learning disorders/disabilities, cerebral palsy. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types:

paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

In another aspect, the eye abnormality is a retinal abnormality. In still another aspect, the eye abnormality is consistent with vision problems or blindness. In yet another aspect, the retinal abnormality is consistent with retinitis pigmentosa or is characterized by retinal degeneration or retinal dysplasia.

5 In still another aspect, the retinal abnormalities are consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schönberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

20 In still another aspect, the eye abnormality is a cataract. In still yet another aspect, the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

25 In still another aspect, the developmental abnormality comprises embryonic lethality or reduced viability.

In still yet another aspect, the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e.g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

35 In still another aspect, the immunological disorders are consistent with systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis;

autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

In still another aspect, the bone metabolic abnormality or disorder is arthritis, osteoporosis, osteopenia or osteopetrosis.

In another aspect, the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin

levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia;

5 increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased

10 in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular

15 hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T

20 cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet

25 count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response

30 to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral

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density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

The invention also provides an isolated cell derived from a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In one aspect, the isolated cell is a murine cell. In yet another aspect, the murine cell is an embryonic stem cell. In still another aspect, the isolated cell is derived from a non-human transgenic animal which exhibits at least one of the following phenotypes compared with gender matched wild-type littermates: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality. The invention also provides a method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980,

PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

- (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;
- (b) measuring a physiological characteristic of the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal;
- (d) administering a test agent to the non-human transgenic animal of (a); and
- (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

In one aspect, the phenotype associated with the gene disruption comprises a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

In yet another aspect, the neurological disorder is an increased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is a decreased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is an abnormal circadian rhythm during home-cage activity testing. In yet another aspect, the neurological disorder is an enhanced motor coordination during inverted screen testing. In yet another aspect, the neurological disorder is impaired motor coordination during inverted screen testing. In yet another aspect, the neurological disorder includes depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety, autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder, enhancement of cognitive function, loss of cognitive function associated with but not limited to Alzheimer's disease, stroke, or traumatic injury to the brain, seizures resulting

from disease or injury including but not limited to epilepsy, learning disorders/disabilities, cerebral palsy. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

5 In yet another aspect, the eye abnormality is a retinal abnormality. In still another aspect, the eye abnormality is consistent with vision problems or blindness. In yet another aspect, the retinal abnormality is consistent with retinitis pigmentosa or is characterized by retinal degeneration or retinal dysplasia.

10 In still another aspect, the retinal abnormalities are consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, 15 Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, 20 Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

In still another aspect, the eye abnormality is a cataract. In still yet another aspect, the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, 25 Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism, or Conradi syndrome.

In still another aspect, the developmental abnormality comprises embryonic lethality or reduced viability.

30 In still another aspect, the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's 35 sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

In still another aspect, the immunological disorders are consistent with systemic lupus erythematosus;

rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus;

5 immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel

10 disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host

15 disease.

In yet another aspect, the bone metabolic abnormality or disorder is arthritis, osteoporosis, osteopenia or osteopetrosis.

In another aspect, the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open

20 field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety

25 phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension

30 testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities;

35 dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum

glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine;

5 glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute

10 lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red

15 blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph

20 nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated

25 T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean

30 serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD);

35 increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight;

decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopenia; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

The invention also provides an agent which modulates the phenotype associated with gene disruption. In one aspect, the agent is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-

PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a method of identifying an agent that modulates a physiological characteristic associated with a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

- (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;
- (b) measuring a physiological characteristic exhibited by the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic exhibited by the non-human transgenic animal that differs from the physiological characteristic exhibited by the wild-type animal is identified as a physiological characteristic associated with gene disruption;
- (d) administering a test agent to the non-human transgenic animal of (a); and
- (e) determining whether the physiological characteristic associated with gene disruption is modulated.

In one aspect, the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open

field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph

nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just

a few ducts; growth retardation with reduced viability; and embryonic lethality.

The invention also provides an agent that modulates a physiological characteristic which is associated with gene disruption. In one aspect, the agent is an agonist or antagonist of the phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agent is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026,

anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a method of identifying an agent which modulates a behavior associated with a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) observing the behavior exhibited by the non-human transgenic animal of (a);

(c) comparing the observed behavior of (b) with that of a gender matched wild-type animal, wherein the observed behavior exhibited by the non-human transgenic animal that differs from the observed behavior exhibited by the wild-type animal is identified as a behavior associated with gene disruption;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the agent modulates the behavior associated with gene disruption.

In one aspect, the observed behavior is an increased anxiety-like response during open field activity testing. In yet another aspect, the observed behavior is a decreased anxiety-like response during open field activity testing. In yet another aspect, the observed behavior is an abnormal circadian rhythm during home-cage activity testing. In yet another aspect, the observed behavior is an enhanced motor coordination during inverted screen testing. In yet another aspect, the observed behavior is impaired motor coordination during inverted screen testing. In yet another aspect, the observed behavior includes depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety, autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood

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PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) administering a test agent to said non-human transgenic animal; and

(c) determining whether the test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality associated with the gene disruption in the non-human transgenic animal.

In yet another aspect, the neurological disorder is an increased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is a decreased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is an abnormal circadian rhythm during home-cage activity testing. In yet another aspect, the neurological disorder is an enhanced motor coordination during inverted screen testing. In yet another aspect, the neurological disorder is impaired motor coordination during inverted screen testing. In yet another aspect, the neurological disorder includes depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder,

schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety, autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder, enhancement of cognitive function, loss of cognitive function associated with but not limited to Alzheimer's disease, stroke, or traumatic injury to the brain, seizures resulting from disease or injury including but not limited to epilepsy, learning disorders/disabilities, cerebral palsy. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

In another aspect, the eye abnormality is a retinal abnormality. In still another aspect, the eye abnormality is consistent with vision problems or blindness. In yet another aspect, the retinal abnormality is consistent with retinitis pigmentosa or is characterized by retinal degeneration or retinal dysplasia.

In still another aspect, the retinal abnormalities the retinal abnormalities are consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

In still another aspect, the eye abnormality is a cataract. In still yet another aspect, the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism, or Conradi syndrome.

In still another aspect, the developmental abnormality comprises embryonic lethality or reduced viability.

In yet another aspect, the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute

myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

In still yet another aspect, the immunological disorders are consistent with systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

In yet another aspect, the bone metabolic abnormality or disorder is arthritis, osteoporosis, osteopenia or osteopetrosis.

In another aspect, the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension

testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; opthamological abnormalities; corneal epidermidalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean

serum TNF-alpha; MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

The invention also provides an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality which is associated with gene disruption. In one aspect, the agent is an agonist or antagonist of the phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423,

PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agent is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a therapeutic agent for the treatment of a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

The invention also provides a method of identifying an agent that modulates the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568,

PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

- 5 (a) contacting a test agent with a host cell expressing a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide; and

- 10 (b) determining whether the test agent modulates the expression of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by the host cell.

- The invention also provides an agent that modulates the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In one aspect, the agent is an agonist or antagonist of the phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agent is an agonist or antagonist of a PRO69122,

PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a method of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which

encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

- (b) measuring a physiological characteristic of the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal;
- (d) administering a test agent to the non-human transgenic animal of (a); and
- (e) evaluating the effects of the test agent on the identified condition associated with gene disruption in the non-human transgenic animal.

In one aspect, the condition is a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

The invention also provides a therapeutic agent which is capable of affecting a condition associated with gene disruption. In one aspect, the agent is an agonist or antagonist of the phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agent is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-

PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a pharmaceutical composition comprising a therapeutic agent capable of affecting the condition associated with gene disruption.

The invention also provides a method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject in need of such treatment whom may already have the disorder, or may be prone to have the disorder or may be in whom the disorder is to be prevented, a therapeutically effective amount of a therapeutic agent, or agonists or antagonists thereof, , thereby effectively treating or preventing or ameliorating said disorder or disease.

In yet another aspect, the neurological disorder is an increased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is a decreased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is an abnormal circadian rhythm during home-cage activity testing. In yet another aspect, the neurological disorder is an enhanced motor coordination

during inverted screen testing. In yet another aspect, the neurological disorder is impaired motor coordination during inverted screen testing. In yet another aspect, the neurological disorder includes depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety, autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder, enhancement of cognitive function, loss of cognitive function associated with but not limited to Alzheimer's disease, stroke, or traumatic injury to the brain, seizures resulting from disease or injury including but not limited to epilepsy, learning disorders/disabilities, cerebral palsy. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

In another aspect, the eye abnormality is a retinal abnormality. In still another aspect, the eye abnormality is consistent with vision problems or blindness. In yet another aspect, the retinal abnormality is consistent with retinitis pigmentosa or is characterized by retinal degeneration or retinal dysplasia.

In still another aspect, the retinal abnormalities are consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotidemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

In still another aspect, the eye abnormality is a cataract. In still yet another aspect, the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

In still another aspect, the developmental abnormality comprises embryonic lethality or reduced viability.

In yet another aspect, the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

In still yet another aspect, the immunological disorders are consistent with systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

In yet another aspect, the bone metabolic abnormality or disorder is arthritis, osteoporosis, osteopenia or osteopetrosis.

In another aspect the therapeutic agent is an agonist or antagonist of the phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agent is an agonist or

antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646,

PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal cell culture, each cell of said culture comprising a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) administering a test agent to said cell culture; and

(c) determining whether the test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in said culture.

In yet another aspect, the neurological disorder is an increased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is a decreased anxiety-like response during open field activity testing. In yet another aspect, the neurological disorder is an abnormal circadian rhythm during home-cage activity testing. In yet another aspect, the neurological disorder is an enhanced motor coordination during inverted screen testing. In yet another aspect, the neurological disorder is impaired motor coordination during inverted screen testing. In yet another aspect, the neurological disorder includes depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety, autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder, enhancement of cognitive function, loss of cognitive function associated with but not limited to Alzheimer's disease, stroke, or traumatic injury to the brain, seizures resulting from disease or injury including but not limited to epilepsy, learning disorders/disabilities, cerebral palsy. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

In another aspect, the eye abnormality is a retinal abnormality. In still another aspect, the eye abnormality is consistent with vision problems or blindness. In yet another aspect, the retinal abnormality is consistent with retinitis pigmentosa or is characterized by retinal degeneration or retinal dysplasia.

In still another aspect, the retinal abnormalities are consistent with retinal dysplasia, various retinopathies,

including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

In still another aspect, the eye abnormality is a cataract. In still yet another aspect, the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

In still another aspect, the developmental abnormality comprises embryonic lethality or reduced viability.

In yet another aspect, the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

In still yet another aspect, the immunological disorders are consistent with systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such

as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria;

5 immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

In yet another aspect, the bone metabolic abnormality or disorder is arthritis, osteoporosis, osteopenia or osteopetrosis.

10 The invention also provides an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality which is associated with gene disruption in said culture. In one aspect, the agent is an agonist or antagonist of the phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222,

15 PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095,

20 PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect, the agent is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384,

25 PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In yet another aspect,

30 the agonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-

35 PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-

PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody. In still another aspect, the antagonist agent is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

The invention also provides a method of modulating a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already have the phenotype, or may be prone to have the phenotype or may be in whom the phenotype is to be prevented, an effective amount of an agent identified as modulating said phenotype, or agonists or antagonists thereof, thereby effectively modulating the phenotype.

The invention also provides a method of modulating a physiological characteristic associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already exhibit the physiological characteristic, or may be prone to exhibit the physiological characteristic or may be in whom the physiological characteristic is to be prevented, an effective amount of an agent identified as modulating said physiological characteristic, or agonists or antagonists thereof, thereby effectively modulating the physiological characteristic.

The invention also provides a method of modulating a behavior associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342,

PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already exhibit the behavior, or may be prone to exhibit the behavior or may be in whom the exhibited behavior is to be prevented, an effective amount of an agent identified as modulating said behavior, or agonists or antagonists thereof, thereby effectively modulating the behavior.

10 The invention also provides a method of modulating the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a host cell expressing said PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, an effective amount of an agent identified as modulating said expression, or agonists or antagonists thereof, thereby effectively modulating the expression of said polypeptide.

The invention also provides a method of modulating a condition associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may have the condition, or may be prone to have the condition or may be in whom the condition is to be prevented, a therapeutically effective amount of a therapeutic agent identified as modulating said condition, or agonists or

antagonists thereof, thereby effectively modulating the condition.

The invention also provides a method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a non-human transgenic animal cell culture, each cell of said culture comprising a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, an effective amount of an agent identified as treating or preventing or ameliorating said disorder, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

B. Further Embodiments

In yet further embodiments, the invention is directed to the following set of potential claims for this application:

1. A method of identifying a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481,

PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

- 5 (b) measuring a physiological characteristic of the non-human transgenic animal; and
- (c) comparing the measured physiological characteristic with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal.
- 10 2. The method of Claim 1, wherein the non-human transgenic animal is heterozygous for the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,
- 15 PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.
- 20 3. The method of Claim 1, wherein the phenotype exhibited by the non-human transgenic animal as compared with gender matched wild-type littermates is at least one of the following: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.
4. The method of Claim 3, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.
- 25 5. The method of Claim 3, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.
6. The method of Claim 3, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.
7. The method of Claim 3, wherein the neurological disorder is an enhanced motor coordination during
- 30 inverted screen testing.
8. The method of Claim 3, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.
9. The method of Claim 3, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia,
- 35 cognitive disorders, hyperalgesia or sensory disorders.
10. The method of Claim 3, wherein the eye abnormality is a retinal abnormality.
11. The method of Claim 3, wherein the eye abnormality is consistent with vision problems or blindness.
12. The method of Claim 10, wherein the retinal abnormality is consistent with retinitis pigmentosa.

13. The method of Claim 10, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.
14. The method of Claim 10, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, 5 corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate 10 atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar 15 atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.
15. The method of Claim 3, wherein the eye abnormality is a cataract.
16. The method of Claim 15, wherein the cataract is consistent with systemic diseases such as human Down's 20 syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.
17. The method of Claim 3, wherein the developmental abnormality comprises embryonic lethality or reduced viability.
18. The method of Claim 3, wherein the cardiovascular, endothelial or angiogenic disorders are arterial 25 diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, 30 telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.
19. The method of Claim 3, wherein the immunological disorders are systemic lupus erythematosus; 35 rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis

(Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

20. The method of Claim 3, wherein the bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

21. The method of Claim 1, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels;

increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional

area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse
 5 abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size;
 10 myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous
 15 tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

22. An isolated cell derived from a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138,
 20 PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201,
 25 PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

23. The isolated cell of Claim 22 which is a murine cell.

24. The isolated cell of Claim 23, wherein the murine cell is an embryonic stem cell.

25. The isolated cell of Claim 22, wherein the non-human transgenic animal exhibits at least one of the following phenotypes compared with gender matched wild-type littermates: a neurological disorder; a
 30 cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

26. A method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190,
 35 PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436,

PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

27. The method of Claim 26, wherein the phenotype associated with the gene disruption comprises a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

28. The method of Claim 27, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

29. The method of Claim 27, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

30. The method of Claim 27, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

31. The method of Claim 27, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

32. The method of Claim 27, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

33. The method of Claim 27, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

34. The method of Claim 27, wherein the eye abnormality is a retinal abnormality.

35. The method of Claim 27, wherein the eye abnormality is consistent with vision problems or blindness.

36. The method of Claim 34, wherein the retinal abnormality is consistent with retinitis pigmentosa.

37. The method of Claim 34, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

38. The method of Claim 34, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

39. The method of Claim 27, wherein the eye abnormality is a cataract.

40. The method of Claim 39, wherein the cataract is consistent with systemic diseases such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

41. The method of Claim 27, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

42. The method of Claim 27, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

43. The method of Claim 27, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis

(Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation-associated diseases including graft rejection and graft-versus-host disease.

44. The method of Claim 27, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.
45. The method of Claim 26, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels;

increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional

area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

46. An agent identified by the method of Claim 26.

47. The agent of Claim 46 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

48. The agent of Claim 47, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

49. The agent of Claim 47, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540,

anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

50. A method of identifying an agent that modulates a physiological characteristic associated with a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) measuring a physiological characteristic exhibited by the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic exhibited by the non-human transgenic animal that differs from the physiological characteristic exhibited by the wild-type animal is identified as a physiological characteristic associated with gene disruption;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the physiological characteristic associated with gene disruption is modulated.

51. The method of Claim 50, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light

phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased

CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen;

5 increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean

10 percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and

15 connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional

20 area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse

25 abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size;

30 myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous

35 tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

52. An agent identified by the method of Claim 50.

53. The agent of Claim 52 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222,

PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

54. The agent of Claim 53, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

55. The agent of Claim 53, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

56. A method of identifying an agent which modulates a behavior associated with a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which

encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) observing the behavior exhibited by the non-human transgenic animal of (a);

(c) comparing the observed behavior of (b) with that of a gender matched wild-type animal, wherein the observed behavior exhibited by the non-human transgenic animal that differs from the observed behavior exhibited by the wild-type animal is identified as a behavior associated with gene disruption;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the agent modulates the behavior associated with gene disruption.

57. The method of Claim 56, wherein the behavior is an increased anxiety-like response during open field activity testing.

58. The method of Claim 56, wherein the behavior is a decreased anxiety-like response during open field activity testing.

59. The method of Claim 56, wherein the behavior is an abnormal circadian rhythm during home-cage activity testing.

60. The method of Claim 56, wherein the behavior is an enhanced motor coordination during inverted screen testing.

61. The method of Claim 56, wherein the behavior is an impaired motor coordination during inverted screen testing.

62. The method of Claim 56, wherein the behavior is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

63. An agent identified by the method of Claim 56.

64. The agent of Claim 63 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

65. The agent of Claim 64, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-

PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

66. The agent of Claim 64, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

67. A method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) administering a test agent to said non-human transgenic animal; and

(c) determining whether said test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in the non-human transgenic animal.

5 68. The method of Claim 67, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

69. The method of Claim 67, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

10 70. The method of Claim 67, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

71. The method of Claim 67, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

72. The method of Claim 67, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

15 73. The method of Claim 73, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

74. The method of Claim 67, wherein the eye abnormality is a retinal abnormality.

75. The method of Claim 67, wherein the eye abnormality is consistent with vision problems or blindness.

20 76. The method of Claim 74, wherein the retinal abnormality is consistent with retinitis pigmentosa.

77. The method of Claim 74, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

25 78. The method of Claim 74, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, 30 Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotidemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

79. The method of Claim 67, wherein the eye abnormality is a cataract.

80. The method of Claim 79, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

5 81. The method of Claim 67, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

82. The method of Claim 67, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

83. The method of Claim 67, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

84. The method of Claim 67, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

85. The method of Claim 67, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open

field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T

cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21^{hi}CD23^{med} B cells in spleen; decrease in Peyer's patch B220⁺ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB⁺ CD38⁺ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220⁺ CD38^{low} and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

86. An agent identified by the method of Claim 67.

المادة 87. The agent of Claim 86 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222,

PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

88. The agent of Claim 87, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

89. The agent of Claim 87, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

90. A therapeutic agent identified by the method of Claim 67.

91. A method of identifying an agent that modulates the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method

comprising:

(a) contacting a test agent with a host cell expressing a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide; and

(b) determining whether the test agent modulates the expression of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by the host cell.

92. An agent identified by the method of Claim 91.

93. The agent of Claim 92 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

94. The agent of Claim 93, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

95. The agent of Claim 93, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-

PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

96. A method of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) evaluating the effects of the test agent on the identified condition associated with gene disruption in the non-human transgenic animal.

97. The method of Claim 96, wherein the condition is a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

98. A therapeutic agent identified by the method of Claim 96.

99. The therapeutic agent of Claim 98 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

100. The therapeutic agent of Claim 99, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

101. The therapeutic agent of Claim 99, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

102. A pharmaceutical composition comprising the therapeutic agent of Claim 98.

103. A method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566,

PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001,

PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject in need of such treatment whom may already have the disorder; or may be prone to have the disorder or may be in whom the disorder is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 94, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

104. The method of Claim 103, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

105. The method of Claim 103, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

106. The method of Claim 103, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

107. The method of Claim 103, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

108. The method of Claim 103, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

109. The method of Claim 103, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

110. The method of Claim 103, wherein the eye abnormality is a retinal abnormality.

111. The method of Claim 103, wherein the eye abnormality is consistent with vision problems or blindness.

112. The method of Claim 110, wherein the retinal abnormality is consistent with retinitis pigmentosa.

113. The method of Claim 110, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

114. The method of Claim 110, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemelia, cystinosis, Wolfram syndrome,

Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

115. The method of Claim 103, wherein the eye abnormality is a cataract.

116. The method of Claim 115, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

117. The method of Claim 103, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

118. The method of Claim 103, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

119. The method of Claim 103, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

120. The method of Claim 103, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

121. A method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone

metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal cell culture, each cell of said culture comprising a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) administering a test agent to said cell culture; and

(c) determining whether said test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in said cell culture.

122. The method of Claim 121, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

123. The method of Claim 121, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

124. The method of Claim 121, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

125. The method of Claim 121, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

126. The method of Claim 121, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

127. The method of Claim 121, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

128. The method of Claim 121, wherein the eye abnormality is a retinal abnormality.

129. The method of Claim 121, wherein the eye abnormality is consistent with vision problems or blindness.

130. The method of Claim 128, wherein the retinal abnormality is consistent with retinitis pigmentosa.

131. The method of Claim 128, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

132. The method of Claim 128, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

133. The method of Claim 121, wherein the eye abnormality is a cataract.

134. The method of Claim 133, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

135. The method of Claim 121, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

136. The method of Claim 121, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

137. The method of Claim 121, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis

(Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

138. The method of Claim 121, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

139. An agent identified by the method of Claim 121.

140. The agent of Claim 139 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

141. The agent of Claim 140, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

142. The agent of Claim 140, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-

PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

143. A therapeutic agent identified by the method of Claim 121.

144. A method of modulating a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already have the phenotype, or may be prone to have the phenotype or may be in whom the phenotype is to be prevented, an effective amount of the agent of Claim 46, or agonists or antagonists thereof, thereby effectively modulating the phenotype.

145. A method of modulating a physiological characteristic associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already exhibit the physiological characteristic, or may be prone to exhibit the physiological characteristic or may be in whom the physiological characteristic is to be prevented, an effective amount of the agent of Claim 52, or agonists or antagonists thereof, thereby effectively modulating the physiological characteristic.

146. A method of modulating a behavior associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203

or PRO35250 polypeptide, the method comprising administering to a subject whom may already exhibit the behavior, or may be prone to exhibit the behavior or may be in whom the exhibited behavior is to be prevented, an effective amount of the agent of Claim 63, or agonists or antagonists thereof, thereby effectively modulating the behavior.

147. A method of modulating the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO285, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a host cell expressing said PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, an effective amount of the agent of Claim 92, or agonists or antagonists thereof, thereby effectively modulating the expression of said polypeptide.

148. A method of modulating a condition associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may have the condition, or may be prone to have the condition or may be in whom the condition is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 98, or agonists or antagonists thereof, thereby effectively modulating the condition.

149. A method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604,

PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a non-human transgenic animal cell culture, each cell of said culture comprising a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, a therapeutically effective amount of the agent of Claim 139, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO69122 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA284870" (UNQ128).

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO204 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA30871-1157" (UNQ178).

Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO214 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA32286-1191" (UNQ188).

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO222 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA33107-1135" (UNQ196).

Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO234 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA35557-1137" (UNQ208).

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID NO:9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO265 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA36350-1158" (UNQ232).

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO309 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA61601-1223" (UNQ272).

5 Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO332 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA40982-1235" (UNQ293).

Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

10 Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO342 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA38649" (UNQ301).

Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

15 Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO356 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA47470-1130P1" (UNQ313).

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO540 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA44189-1322" (UNQ341).

20 Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO618 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA49152-1324" (UNQ354).

25 Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO944 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA52185-1370" (UNQ481).

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

30 Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO994 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA58855-1422" (UNQ518).

Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.

35 Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO1079 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA56050-1455" (UNQ536).

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO1110 cDNA, wherein

SEQ ID NO:31 is a clone designated herein as "DNA58727-1474" (UNQ553).

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO1122 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA62377-1381-1" (UNQ561).

5 Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO1138 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA58850-1495" (UNQ576).

10 Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO1190 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA59586-1520" (UNQ604).

Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

15 Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO1272 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA64896-1539" (UNQ642).

Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

20 Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO1286 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA64903-1553" (UNQ655).

Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO1295 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA59218-1559" (UNQ664).

25 Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO1309 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA59588-1571" (UNQ675).

30 Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO1316 cDNA, wherein SEQ ID NO:47 is a clone designated herein as "DNA60608-1577" (UNQ682).

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

35 Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO1383 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA58743-1609" (UNQ719).

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO1384 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA71159-1617" (UNQ721).

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

5 Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO1431 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA73401-1633" (UNQ737).

Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO1434 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA68818-2536" (UNQ739).

10 Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO1475 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA61185-1646" (UNQ746).

15 Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO1481 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA58732-1650" (UNQ750).

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

20 Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO1568 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA68880-1676" (UNQ774).

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

25 Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO1573 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA73735-1681" (UNQ779).

Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO1599 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA62845-1684" (UNQ782).

30 Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO1604 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA71286-1687" (UNQ785).

35 Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO1605 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA77648-1688" (UNQ786).

Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ

ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO1693 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA77301-1708" (UNQ803).

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

5 Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO1753 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA68883-1691" (UNQ826).

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

10 Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO1755 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA76396-1698" (UNQ828).

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO1777 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA71235-1706" (UNQ839).

15 Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO1788 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA77652-2505" (UNQ850).

20 Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO1864 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA45409-2511" (UNQ855).

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

25 Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO1925 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA82302-2529" (UNQ904).

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:83 shown in Figure 83.

30 Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO1926 cDNA, wherein SEQ ID NO:85 is a clone designated herein as "DNA82340-2530" (UNQ905).

Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO3566 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA59844-2542" (UNQ1840).

35 Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO4330 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA90842-2574" (UNQ1886).

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO4423 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA96893-2621" (UNQ1940).

5 Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO36935 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA336539" (UNQ2257).

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

10 Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO4977 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA62849-2647" (UNQ2420).

Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

15 Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO4979 cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA222844" (UNQ2421).

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO4980 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA97003-2649" (UNQ2422).

20 Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO4981 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA94849-2960" (UNQ2423).

25 Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO5801 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA115291-2681" (UNQ2501).

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

30 Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO5995 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA96988-2685" (UNQ2507).

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

35 Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO6001 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA98380" (UNQ2512).

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO6095 cDNA,

wherein SEQ ID NO:109 is a clone designated herein as "DNA105680-2710" (UNQ2543).

Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO6182 cDNA, wherein SEQ ID NO:111 is a clone designated herein as "DNA110700-2716" (UNQ2553).

5 Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO7170 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "DNA108722-2743" (UNQ2782).

10 Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO7171 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA108670-2744" (UNQ2783).

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

15 Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO7436 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA119535-2756" (UNQ2973).

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

20 Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO9912 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA108700-2802" (UNQ3077).

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO9917 cDNA, wherein SEQ ID NO:121 is a clone designated herein as "DNA119474-2803" (UNQ3079).

25 Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO37337 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA226874" (UNQ5291).

30 Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO37496 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA227033" (UNQ5407).

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

35 Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO19646 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA145841-2868" (UNQ5827).

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO21718 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA188342" (UNQ5893):

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

5 Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO19820 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA149911-2885" (UNQ5926).

Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO21201 cDNA, wherein SEQ ID NO:133 is a clone designated herein as "DNA168028-2956" (UNQ6098).

10 Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO20026 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA154095-2998" (UNQ6115).

15 Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO20110 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA166819-1381R1P1" (UNQ6129).

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

20 Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO23203 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA185171-2994" (UNQ6507).

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

25 Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO35250 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA171732-3100" (UNQ9574).

Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

30 I. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence
35 polypeptides and polypeptide variants (which are further defined herein). The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604,

PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

A "native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide derived from nature. Such native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788,

PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. The invention provides native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides disclosed herein which are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171,

PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides.

The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide "extracellular domain" or "ECD" refers to a form of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122,

PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide variant" means a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423,

PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, preferably an active PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718; PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, as defined herein having at least about 80% amino acid sequence identity with a full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926,

PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide). Such PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide variants include, for instance, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide variant will have or will have at least about 80% amino acid sequence identity, alternatively will have or will have at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to a full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994,

PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein. Ordinarily, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polypeptides are or are at least about 10 amino acids in length, alternatively are or are at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210,

220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more. Optionally, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polypeptides will have no more than one conservative amino acid substitution as compared to the native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence, alternatively will have or will have no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to the native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence.

"Percent (%) amino acid sequence identity" with respect to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434,

PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence, after aligning the sequences and

5 introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms

10 needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559,

15 where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

20 In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

25
$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid

30 sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence

35 of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X," "Y" and "Z" each represent different hypothetical amino acid residues. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

"PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polynucleotide" or "PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant nucleic acid sequence" means a nucleic acid molecule which encodes a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, preferably an active PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, as defined herein and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein, a full-length native

sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide). Ordinarily, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110,

PRO23203 or PRO35250 variant polynucleotide will have or will have at least about 80% nucleic acid sequence identity, alternatively will have or will have at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein, a full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475,

PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polynucleotides are or are at least about 5 nucleotides in length, alternatively are or are at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

"Percent (%) nucleic acid sequence identity" with respect to PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available

through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides. Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

The invention also provides PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polynucleotides which are nucleic acid molecules that encode a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO69122, PRO204, PRO214,

PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as disclosed herein. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polypeptides may be those that are encoded by a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant polynucleotide.

The term "full-length coding region" when used in reference to a nucleic acid encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide refers to the sequence of nucleotides which encode the full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide of the invention (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures).

The term "full-length coding region" when used in reference to an ATCC deposited nucleic acid refers to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-encoding portion of the cDNA that is inserted into the vector deposited with the ATCC (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures).

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. The invention provides that the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-

encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above.

An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

5 The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, 10 PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide 15 to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

 "Active" or "activity" for the purposes herein refers to form(s) of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, 20 PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, 25 PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, 30 PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally- 35 occurring PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788,

PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

The term "antagonist" is used in the broadest sense [unless otherwise qualified], and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense [unless otherwise qualified] and includes any molecule that mimics a biological activity of a native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide disclosed

herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may comprise contacting a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

"Treating" or "treatment" or "alleviation" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. A subject in need of treatment may already have the disorder, or may be prone to have the disorder or may be in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an

acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, rodents such as rats or mice, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

5 Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; 10 low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming 15 counterions such as sodium; and/or nonionic surfactants such as TWEENTM, polyethylene glycol (PEG), and PLURONICSTM.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. 20 Depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, 25 PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, 30 PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

35 An "effective amount" of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755,

PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptide, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecule or an agonist or antagonist thereof as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated purpose.

The term "therapeutically effective amount" refers to an amount of an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-

PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptide, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecule or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. See the definition herein of "treating". To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic.

The phrases "cardiovascular, endothelial and angiogenic disorder", "cardiovascular, endothelial and angiogenic dysfunction", "cardiovascular, endothelial or angiogenic disorder" and "cardiovascular, endothelial or angiogenic dysfunction" are used interchangeably and refer in part to systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins, and/or lymphatics. This would include indications that stimulate angiogenesis and/or cardiovascularization, and those that inhibit angiogenesis and/or cardiovascularization. Such disorders include, for example, arterial disease, such as atherosclerosis, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and

lymphedema; and other vascular disorders such as peripheral vascular disease, cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma, tumor angiogenesis, trauma such as wounds, burns, and other injured tissue, implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, or osteoporosis. This would also include angina, myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as CHF.

"Hypertrophy", as used herein, is defined as an increase in mass of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of an organ or tissue is due either to an increase in the mass of the individual cells (true hypertrophy), or to an increase in the number of cells making up the tissue (hyperplasia), or both. Certain organs, such as the heart, lose the ability to divide shortly after birth. Accordingly, "cardiac hypertrophy" is defined as an increase in mass of the heart, which, in adults, is characterized by an increase in myocyte cell size and contractile protein content without concomitant cell division. The character of the stress responsible for inciting the hypertrophy, (*e.g.*, increased preload, increased afterload, loss of myocytes, as in myocardial infarction, or primary depression of contractility), appears to play a critical role in determining the nature of the response. The early stage of cardiac hypertrophy is usually characterized morphologically by increases in the size of myofibrils and mitochondria, as well as by enlargement of mitochondria and nuclei. At this stage, while muscle cells are larger than normal, cellular organization is largely preserved. At a more advanced stage of cardiac hypertrophy, there are preferential increases in the size or number of specific organelles, such as mitochondria, and new contractile elements are added in localized areas of the cells, in an irregular manner. Cells subjected to long-standing hypertrophy show more obvious disruptions in cellular organization, including markedly enlarged nuclei with highly lobulated membranes, which displace adjacent myofibrils and cause breakdown of normal Z-band registration. The phrase "cardiac hypertrophy" is used to include all stages of the progression of this condition, characterized by various degrees of structural damage of the heart muscle, regardless of the underlying cardiac disorder. Hence, the term also includes physiological conditions instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Heart failure" refers to an abnormality of cardiac function where the heart does not pump blood at the rate needed for the requirements of metabolizing tissues. The heart failure can be caused by a number of factors, including ischemic, congenital, rheumatic, or idiopathic forms.

"Congestive heart failure" (CHF) is a progressive pathologic state where the heart is increasingly unable to supply adequate cardiac output (the volume of blood pumped by the heart over time) to deliver the oxygenated blood to peripheral tissues. As CHF progresses, structural and hemodynamic damages occur. While these damages have a variety of manifestations, one characteristic symptom is ventricular hypertrophy. CHF is a common end result of a number of various cardiac disorders.

"Myocardial infarction" generally results from atherosclerosis of the coronary arteries, often with superimposed coronary thrombosis. It may be divided into two major types: transmural infarcts, in which myocardial necrosis involves the full thickness of the ventricular wall, and subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both, without extending all the way through the ventricular wall to the epicardium. Myocardial infarction is known to cause both a change in

hemodynamic effects and an alteration in structure in the damaged and healthy zones of the heart. Thus, for example, myocardial infarction reduces the maximum cardiac output and the stroke volume of the heart. Also associated with myocardial infarction is a stimulation of the DNA synthesis occurring in the interstice as well as an increase in the formation of collagen in the areas of the heart not affected.

5 As a result of the increased stress or strain placed on the heart in prolonged hypertension due, for example, to the increased total peripheral resistance, cardiac hypertrophy has long been associated with "hypertension". A characteristic of the ventricle that becomes hypertrophic as a result of chronic pressure overload is an impaired diastolic performance. Fouad *et al.*, J. Am. Coll. Cardiol., 4: 1500-1506 (1984); Smith *et al.*, J. Am. Coll. Cardiol., 5: 869-874 (1985). A prolonged left ventricular relaxation has been detected in early essential hypertension, in spite of normal or supranormal systolic function. Hartford *et al.*, Hypertension, 6: 329-338
10 (1984). However, there is no close parallelism between blood pressure levels and cardiac hypertrophy. Although improvement in left ventricular function in response to antihypertensive therapy has been reported in humans, patients variously treated with a diuretic (hydrochlorothiazide), a β -blocker (propranolol), or a calcium channel blocker (diltiazem), have shown reversal of left ventricular hypertrophy, without improvement in diastolic function. Inouye *et al.*, Am. J. Cardiol., 53: 1583-7 (1984).

15 Another complex cardiac disease associated with cardiac hypertrophy is "hypertrophic cardiomyopathy". This condition is characterized by a great diversity of morphologic, functional, and clinical features (Maron *et al.*, N. Engl. J. Med., 316: 780-789 (1987); Spirito *et al.*, N. Engl. J. Med., 320: 749-755 (1989); Louie and Edwards, Prog. Cardiovasc. Dis., 36: 275-308 (1994); Wigle *et al.*, Circulation, 92: 1680-1692 (1995)), the heterogeneity of which is accentuated by the fact that it afflicts patients of all ages. Spirito *et al.*, N. Engl. J. Med., 336: 775-785
20 (1997). The causative factors of hypertrophic cardiomyopathy are also diverse and little understood. In general, mutations in genes encoding sarcomeric proteins are associated with hypertrophic cardiomyopathy. Recent data suggest that β -myosin heavy chain mutations may account for approximately 30 to 40 percent of cases of familial hypertrophic cardiomyopathy. Watkins *et al.*, N. Engl. J. Med., 326: 1108-1114 (1992); Schwartz *et al.*, Circulation, 91: 532-540 (1995); Marian and Roberts, Circulation, 92: 1336-1347 (1995); Thierfelder *et al.*, Cell,
25 77: 701-712 (1994); Watkins *et al.*, Nat. Gen., 11: 434-437 (1995). Besides β -myosin heavy chain, other locations of genetic mutations include cardiac troponin T, alpha topomyosin, cardiac myosin binding protein C, essential myosin light chain, and regulatory myosin light chain. See, Malik and Watkins, Curr. Opin. Cardiol., 12: 295-302 (1997).

30 Supravalvular "aortic stenosis" is an inherited vascular disorder characterized by narrowing of the ascending aorta, but other arteries, including the pulmonary arteries, may also be affected. Untreated aortic stenosis may lead to increased intracardiac pressure resulting in myocardial hypertrophy and eventually heart failure and death. The pathogenesis of this disorder is not fully understood, but hypertrophy and possibly hyperplasia of medial smooth muscle are prominent features of this disorder. It has been reported that molecular variants of the elastin gene are involved in the development and pathogenesis of aortic stenosis. U.S. Patent No.
35 5,650,282 issued July 22, 1997.

"Valvular regurgitation" occurs as a result of heart diseases resulting in disorders of the cardiac valves. Various diseases, like rheumatic fever, can cause the shrinking or pulling apart of the valve orifice, while other diseases may result in endocarditis, an inflammation of the endocardium or lining membrane of the atrioventricular

orifices and operation of the heart. Defects such as the narrowing of the valve stenosis or the defective closing of the valve result in an accumulation of blood in the heart cavity or regurgitation of blood past the valve. If uncorrected, prolonged valvular stenosis or insufficiency may result in cardiac hypertrophy and associated damage to the heart muscle, which may eventually necessitate valve replacement.

5 The term "immune related disease" means a disease in which a component of the immune system of a mammal causes, mediates or otherwise contributes to a morbidity in the mammal. Also included are diseases in which stimulation or intervention of the immune response has an ameliorative effect on progression of the disease. Included within this term are immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, etc.

10 The term "T cell mediated disease" means a disease in which T cells directly or indirectly mediate or otherwise contribute to a morbidity in a mammal. The T cell mediated disease may be associated with cell mediated effects, lymphokine mediated effects, etc., and even effects associated with B cells if the B cells are stimulated, for example, by the lymphokines secreted by T cells.

"Autoimmune disease" can be an organ-specific disease (i.e., the immune response is specifically directed against an organ system such as the endocrine system, the hematopoietic system, the skin, the cardiopulmonary system, the gastrointestinal and liver systems, the renal system, the thyroid, the ears, the neuromuscular system, the central nervous system, etc.) or a systemic disease which can affect multiple organ systems (for example, systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyositis, etc.). Preferred such diseases include autoimmune rheumatologic disorders (such as, for example, rheumatoid arthritis, Sjögren's syndrome, scleroderma, lupus such as SLE and lupus nephritis, polymyositis/dermatomyositis, cryoglobulinemia, anti-phospholipid antibody syndrome, and psoriatic arthritis), autoimmune gastrointestinal and liver disorders (such as, for example, inflammatory bowel diseases (e.g., ulcerative colitis and Crohn's disease), autoimmune gastritis and pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and celiac disease), vasculitis (such as, for example, ANCA-associated vasculitis, including Churg-Strauss vasculitis, Wegener's granulomatosis, and polyarteritis), autoimmune neurological disorders (such as, for example, multiple sclerosis, opsoclonus myoclonus syndrome, myasthenia gravis, neuromyelitis optica, Parkinson's disease, Alzheimer's disease, and autoimmune polyneuropathies), renal disorders (such as, for example, glomerulonephritis, Goodpasture's syndrome, and Berger's disease), autoimmune dermatologic disorders (such as, for example, psoriasis, urticaria, hives, pemphigus vulgaris, bullous pemphigoid, and cutaneous lupus erythematosus), hematologic disorders (such as, for example, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, post-transfusion purpura, and autoimmune hemolytic anemia), atherosclerosis, uveitis, autoimmune hearing diseases (such as, for example, inner ear disease and hearing loss), Behcet's disease, Raynaud's syndrome, organ transplant, and autoimmune endocrine disorders (such as, for example, diabetic-related autoimmune diseases such as insulin-dependent diabetes mellitus (IDDM), Addison's disease, and autoimmune thyroid disease (e.g., Graves' disease and thyroiditis)). More preferred such diseases include, for example, rheumatoid arthritis, ulcerative colitis, ANCA-associated vasculitis, lupus, multiple sclerosis, Sjögren's syndrome, Graves' disease, IDDM, pernicious anemia, thyroiditis, and glomerulonephritis.

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Specific examples of other autoimmune diseases as defined herein, which in some cases encompass those listed above, include, but are not limited to, arthritis (acute and chronic, rheumatoid arthritis including

juvenile-onset rheumatoid arthritis and stages such as rheumatoid synovitis, gout or gouty arthritis, acute immunological arthritis, chronic inflammatory arthritis, degenerative arthritis, type II collagen-induced arthritis, infectious arthritis, Lyme arthritis, proliferative arthritis, psoriatic arthritis, Still's disease, vertebral arthritis, osteoarthritis, arthritis chronica progrediente, arthritis deformans, polyarthritis chronica primaria, reactive arthritis, menopausal arthritis, estrogen-depletion arthritis, and ankylosing spondylitis/rheumatoid spondylitis), autoimmune lymphoproliferative disease, inflammatory hyperproliferative skin diseases, psoriasis such as plaque psoriasis, guttate psoriasis, pustular psoriasis, and psoriasis of the nails, atopy including atopic diseases such as hay fever and Job's syndrome, dermatitis including contact dermatitis, chronic contact dermatitis, exfoliative dermatitis, allergic dermatitis, allergic contact dermatitis, hives, dermatitis herpetiformis, nummular dermatitis, seborrheic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, and atopic dermatitis, x-linked hyper IgM syndrome, allergic intraocular inflammatory diseases, urticaria such as chronic allergic urticaria and chronic idiopathic urticaria, including chronic autoimmune urticaria, myositis, polymyositis/dermatomyositis, juvenile dermatomyositis, toxic epidermal necrolysis, scleroderma (including systemic scleroderma), sclerosis such as systemic sclerosis, multiple sclerosis (MS) such as spino-optical MS, primary progressive MS (PPMS), and relapsing remitting MS (RRMS), progressive systemic sclerosis, atherosclerosis, arteriosclerosis, sclerosis disseminata, ataxic sclerosis, neuromyelitis optica (NMO), inflammatory bowel disease (IBD) (for example, Crohn's disease, autoimmune-mediated gastrointestinal diseases, gastrointestinal inflammation, colitis such as ulcerative colitis, colitis ulcerosa, microscopic colitis, collagenous colitis, colitis polyposa, necrotizing enterocolitis, and transmural colitis, and autoimmune inflammatory bowel disease), bowel inflammation, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, respiratory distress syndrome, including adult or acute respiratory distress syndrome (ARDS), meningitis, inflammation of all or part of the uvea, iritis, choroiditis, an autoimmune hematological disorder, graft-versus-host disease, angioedema such as hereditary angioedema, cranial nerve damage as in meningitis, herpes gestationis, pemphigoid gestationis, pruritis scroti, autoimmune premature ovarian failure, sudden hearing loss due to an autoimmune condition, IgE-mediated diseases such as anaphylaxis and allergic and atopic rhinitis, encephalitis such as Rasmussen's encephalitis and limbic and/or brainstem encephalitis, uveitis, such as anterior uveitis, acute anterior uveitis, granulomatous uveitis, nongranulomatous uveitis, phacoantigenic uveitis, posterior uveitis, or autoimmune uveitis, glomerulonephritis (GN) with and without nephrotic syndrome such as chronic or acute glomerulonephritis such as primary GN, immune-mediated GN, membranous GN (membranous nephropathy), idiopathic membranous GN or idiopathic membranous nephropathy, membrano- or membranous proliferative GN (MPGN), including Type I and Type II, and rapidly progressive GN (RPGN), proliferative nephritis, autoimmune polyglandular endocrine failure, balanitis including balanitis circumscripta plasmacellularis, balanoposthitis, erythema annulare centrifugum, erythema dyschromicum perstans, erythema multiform, granuloma annulare, lichen nitidus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen spinulosus, lichen planus, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant keratosis, pyoderma gangrenosum, allergic conditions and responses, food allergies, drug allergies, insect allergies, rare allergic disorders such as mastocytosis, allergic reaction, eczema including allergic or atopic eczema, asteatotic eczema, dyshidrotic eczema, and vesicular palmoplantar eczema, asthma such as asthma bronchiale, bronchial asthma, and auto-immune asthma, conditions involving infiltration of T cells and chronic inflammatory responses, immune reactions against foreign antigens such as fetal A-B-O blood groups during

pregnancy, chronic pulmonary inflammatory disease, autoimmune myocarditis, leukocyte adhesion deficiency, lupus, including lupus nephritis, lupus cerebritis, pediatric lupus, non-renal lupus, extra-renal lupus, discoid lupus and discoid lupus erythematosus, alopecia lupus, SLE, such as cutaneous SLE or subacute cutaneous SLE, neonatal lupus syndrome (NLE), and lupus erythematosus disseminatus, juvenile onset (Type I) diabetes mellitus, including pediatric IDDM, adult onset diabetes mellitus (Type II diabetes), autoimmune diabetes, idiopathic diabetes insipidus, diabetic retinopathy, diabetic nephropathy, diabetic colitis, diabetic large-artery disorder, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, tuberculosis, sarcoidosis, granulomatosis including lymphomatoid granulomatosis, Wegener's granulomatosis, agranulocytosis, vasculitides, including vasculitis, large-vessel vasculitis (including polymyalgia rheumatica and giant-cell (Takayasu's) arteritis), medium-vessel vasculitis (including Kawasaki's disease and polyarteritis nodosa/periarteritis nodosa), microscopic polyarteritis, immunovascularitis, CNS vasculitis, cutaneous vasculitis, hypersensitivity vasculitis, necrotizing vasculitis such as systemic necrotizing vasculitis, and ANCA-associated vasculitis, such as Churg-Strauss vasculitis or syndrome (CSS) and ANCA-associated small-vessel vasculitis, temporal arteritis, aplastic anemia, autoimmune aplastic anemia, Coombs positive anemia, Diamond Blackfan anemia, hemolytic anemia or immune hemolytic anemia including autoimmune hemolytic anemia (AIHA), pernicious anemia (anemia perniosa), Addison's disease, pure red cell anemia or aplasia (PRCA), Factor VIII deficiency, hemophilia A, autoimmune neutropenia(s), cytopenias such as pancytopenia, leukopenia, diseases involving leukocyte diapedesis, CNS inflammatory disorders, Alzheimer's disease, Parkinson's disease, multiple organ injury syndrome such as those secondary to septicemia, trauma or hemorrhage, antigen-antibody complex-mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, motoneuritis, allergic neuritis, Behçet's disease/syndrome, Castleman's syndrome, Goodpasture's syndrome, Reynaud's syndrome, Sjögren's syndrome, Stevens-Johnson syndrome, pemphigoid such as pemphigoid bullous and skin pemphigoid, pemphigus (including pemphigus vulgaris, pemphigus foliaceus, pemphigus mucus-membrane pemphigoid, and pemphigus erythematosus), autoimmune polyendocrinopathies, Reiter's disease or syndrome, thermal injury due to an autoimmune condition, preeclampsia, an immune complex disorder such as immune complex nephritis, antibody-mediated nephritis, neuroinflammatory disorders, polyneuropathies, chronic neuropathy such as IgM polyneuropathies or IgM-mediated neuropathy, thrombocytopenia (as developed by myocardial infarction patients, for example), including thrombotic thrombocytopenic purpura (TTP), post-transfusion purpura (PTP), heparin-induced thrombocytopenia, and autoimmune or immune-mediated thrombocytopenia including, for example, idiopathic thrombocytopenic purpura (ITP) including chronic or acute ITP, scleritis such as idiopathic cerato-scleritis, episcleritis, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism, hypoparathyroidism, autoimmune endocrine diseases including thyroiditis such as autoimmune thyroiditis, Hashimoto's disease, chronic thyroiditis (Hashimoto's thyroiditis), or subacute thyroiditis, autoimmune thyroid disease, idiopathic hypothyroidism, Grave's disease, polyglandular syndromes such as autoimmune polyglandular syndromes, for example, type I (or polyglandular endocrinopathy syndromes), paraneoplastic syndromes, including neurologic paraneoplastic syndromes such as Lambert-Eaton myasthenic syndrome or Eaton-Lambert syndrome, stiff-man or stiff-person syndrome, encephalomyelitis such as allergic encephalomyelitis or encephalomyelitis allergica and experimental allergic encephalomyelitis (EAE), myasthenia gravis such as thymoma-associated myasthenia gravis, cerebellar

degeneration, neuromyotonia, opsoclonus or opsoclonus myoclonus syndrome (OMS), and sensory neuropathy, multifocal motor neuropathy, Sheehan's syndrome, autoimmune hepatitis, chronic hepatitis, lupoid hepatitis, giant-cell hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis, pneumonitis such as lymphoid interstitial pneumonitis (LIP), bronchiolitis obliterans (non-transplant) vs NSIP, Guillain-Barré syndrome, Berger's disease (IgA nephropathy), idiopathic IgA nephropathy, linear IgA dermatosis, acute febrile neutrophilic dermatosis, subcorneal pustular dermatosis, transient acantholytic dermatosis, cirrhosis such as primary biliary cirrhosis and pneumonocirrhosis, autoimmune enteropathy syndrome, Celiac or Coeliac disease, celiac sprue (gluten enteropathy), refractory sprue, idiopathic sprue, cryoglobulinemia such as mixed cryoglobulinemia, amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), coronary artery disease, autoimmune ear disease such as autoimmune inner ear disease (AIED), autoimmune hearing loss, polychondritis such as refractory or relapsed or relapsing polychondritis, pulmonary alveolar proteinosis, Cogan's syndrome/nonsyphilitic interstitial keratitis, Bell's palsy, Sweet's disease/syndrome, rosacea autoimmune, zoster-associated pain, amyloidosis, a non-cancerous lymphocytosis, a primary lymphocytosis, which includes monoclonal B cell lymphocytosis (e.g., benign monoclonal gammopathy and monoclonal gammopathy of undetermined significance, MGUS), peripheral neuropathy, paraneoplastic syndrome, channelopathies such as epilepsy, migraine, arrhythmia, muscular disorders, deafness, blindness, periodic paralysis, and channelopathies of the CNS, autism, inflammatory myopathy, focal or segmental or focal segmental glomerulosclerosis (FSGS), endocrine ophthalmopathy, uveoretinitis, chorioretinitis, autoimmune hepatological disorder, fibromyalgia, multiple endocrine failure, Schmidt's syndrome, adrenalitis, gastric atrophy, presenile dementia, demyelinating diseases such as autoimmune demyelinating diseases and chronic inflammatory demyelinating polyneuropathy, Dressler's syndrome, alopecia areata, alopecia totalis, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), male and female autoimmune infertility, e.g., due to anti-spermatozoan antibodies, mixed connective tissue disease, Chagas' disease, rheumatic fever, recurrent abortion, farmer's lung, erythema multiforme, post-cardiotomy syndrome, Cushing's syndrome, bird-fancier's lung, allergic granulomatous angiitis, benign lymphocytic angiitis, Alport's syndrome, alveolitis such as allergic alveolitis and fibrosing alveolitis, interstitial lung disease, transfusion reaction, leprosy, malaria, parasitic diseases such as leishmaniasis, kypanosomiasis, schistosomiasis, ascariasis, aspergillosis, Sampter's syndrome, Caplan's syndrome, dengue, endocarditis, endomyocardial fibrosis, diffuse interstitial pulmonary fibrosis, interstitial lung fibrosis, fibrosing mediastinitis, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, endophthalmitis, erythema elevatum et diutinum, erythroblastosis fetalis, eosinophilic facitis, Shulman's syndrome, Felty's syndrome, flariasis, cyclitis such as chronic cyclitis, heterochronic cyclitis, iridocyclitis (acute or chronic), or Fuch's cyclitis, Henoch-Schonlein purpura, human immunodeficiency virus (HIV) infection, SCID, acquired immune deficiency syndrome (AIDS), echovirus infection, sepsis (systemic inflammatory response syndrome (SIRS)), endotoxemia, pancreatitis, thyrotoxicosis, parvovirus infection, rubella virus infection, post-vaccination syndromes, congenital rubella infection, Epstein-Barr virus infection, mumps, Evan's syndrome, autoimmune gonadal failure, Sydenham's chorea, post-streptococcal nephritis, thromboangitis obliterans, thyrotoxicosis, tabes dorsalis, chorioiditis, giant-cell polymyalgia, chronic hypersensitivity pneumonitis, conjunctivitis, such as vernal catarrh, keratoconjunctivitis sicca, and epidemic keratoconjunctivitis, idiopathic nephritic syndrome, minimal change nephropathy, benign familial and ischemia-reperfusion injury, transplant organ reperfusion, retinal autoimmunity, joint inflammation, bronchitis,

chronic obstructive airway/pulmonary disease, silicosis, aphthae, aphthous stomatitis, arteriosclerotic disorders (cerebral vascular insufficiency) such as arteriosclerotic encephalopathy and arteriosclerotic retinopathy, aspermiogenese, autoimmune hemolysis, Boeck's disease, cryoglobulinemia, Dupuytren's contracture, endophthalmia phacoanaphylactica, enteritis allergica, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, Hamman-Rich's disease, sensoneural hearing loss, haemoglobinuria

5 paroxysmatica, hypogonadism, ileitis regionalis, leucopenia, mononucleosis infectiosa, traverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia symphatica, orchitis granulomatosa, pancreatitis, polyradiculitis acuta, pyoderma gangrenosum, Quervain's thyreoiditis, acquired spenic atrophy, non-malignant thymoma, lymphofollicular thymitis, vitiligo, toxic-shock syndrome, food poisoning, conditions involving infiltration of T cells, leukocyte-adhesion deficiency, immune responses associated with acute and delayed hypersensitivity

10 mediated by cytokines and T-lymphocytes, diseases involving leukocyte diapedesis, multiple organ injury syndrome, antigen-antibody complex-mediated diseases, antiglomerular basement membrane disease, autoimmune polyendocrinopathies, oophoritis, primary myxedema, autoimmune atrophic gastritis, sympathetic ophthalmia, rheumatic diseases, mixed connective tissue disease, nephrotic syndrome, insulitis, polyendocrine failure, autoimmune polyglandular syndromes, including polyglandular syndrome type I, adult-onset idiopathic

15 hypoparathyroidism (AOIH), cardiomyopathy such as dilated cardiomyopathy, epidermolysis bullosa acquisita (EBA), hemochromatosis, myocarditis, nephrotic syndrome, primary sclerosing cholangitis, purulent or nonpurulent sinusitis, acute or chronic sinusitis, ethmoid, frontal, maxillary, or sphenoid sinusitis, allergic sinusitis, an eosinophil-related disorder such as eosinophilia, pulmonary infiltration eosinophilia, eosinophilia-myalgia syndrome, Löffler's syndrome, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia,

20 bronchopneumonic aspergillosis, aspergilloma, or granulomas containing eosinophils, anaphylaxis, spondyloarthropathies, seronegative spondyloarthritis, polyendocrine autoimmune disease, sclerosing cholangitis, sclera, episclera, chronic mucocutaneous candidiasis, Bruton's syndrome, transient hypogammaglobulinemia of infancy, Wiskott-Aldrich syndrome, ataxia telangiectasia syndrome, angiectasis, autoimmune disorders associated with collagen disease, rheumatism such as chronic arthrorheumatism,

25 lymphadenitis, reduction in blood pressure response, vascular dysfunction, tissue injury, cardiovascular ischemia, hyperalgesia, renal ischemia, cerebral ischemia, and disease accompanying vascularization, allergic hypersensitivity disorders, glomerulonephritides, reperfusion injury, ischemic re-perfusion disorder, reperfusion injury of myocardial or other tissues, lymphomatous tracheobronchitis, inflammatory dermatoses, dermatoses with acute inflammatory components, multiple organ failure, bullous diseases, renal cortical necrosis, acute purulent

30 meningitis or other central nervous system inflammatory disorders, ocular and orbital inflammatory disorders, granulocyte transfusion-associated syndromes, cytokine-induced toxicity, narcolepsy, acute serious inflammation, chronic intractable inflammation, pyelitis, endarterial hyperplasia, peptic ulcer, valvulitis, and endometriosis.

The phrase "anxiety related disorders" refers to disorders of anxiety, mood, and substance abuse, including but not limited to: depression, generalized anxiety disorders, attention deficit disorder, sleep disorder,

35 hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Such disorders include the mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, social anxiety,

autism, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, monopolar disorders, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder, enhancement of cognitive function, loss of cognitive function associated with but not limited to Alzheimer's disease, stroke, or traumatic injury to the brain, seizures resulting from disease or injury including but not limited to epilepsy, learning disorders/disabilities, cerebral palsy. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

The term "lipid metabolic disorder" refers to abnormal clinical chemistry levels of cholesterol and triglycerides, wherein elevated levels of these lipids is an indication for atherosclerosis. Additionally, abnormal serum lipid levels may be an indication of various cardiovascular diseases including hypertension, stroke, coronary artery diseases, diabetes and/or obesity.

The phrase "eye abnormality" refers to such potential disorders of the eye as they may be related to atherosclerosis or various ophthalmological abnormalities. Such disorders include but are not limited to the following: retinal dysplasia, various retinopathies, restenosis, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinememia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis. Cataracts are also considered an eye abnormality and are associated with such systemic diseases as: Human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15 condition, Alport syndrome, myotonic dystrophy, Fabry disease, hypothyroidisms, or Conradi syndrome. Other ocular developmental anomalies include: Aniridia, anterior segment and dysgenesis syndrome. Cataracts may also occur as a result of an intraocular infection or inflammation (uveitis).

A "growth inhibitory amount" of an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-

PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptide or PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecule is an amount capable of inhibiting the growth of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "growth inhibitory amount" of an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788,

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A "cytotoxic amount" of an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316,

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10 PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecule is an amount capable of causing the destruction of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "cytotoxic amount" of an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356,
15 anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618,
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PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody compositions with polypeptopic specificity, polyclonal antibodies, single chain anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-

PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies, and fragments of anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies (see below) as long as they exhibit the desired biological or immunological activity. The term "immunoglobulin" (Ig) is used interchangeable with antibody herein.

An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. The invention provides that the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain ($C_H 1$). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , ϵ , γ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and define specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L , and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the V_H ; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L , and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H ; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler et al., Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, e.g., U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be

isolated from phage antibody libraries using the techniques described in Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991), for example.

The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Patent No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

An "intact" antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, C_H 1, C_H 2 and C_H 3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H 1). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large F(ab')₂ fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_H 1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an

antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

"Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992).

A "species-dependent antibody," e.g., a mammalian anti-human IgE antibody, is an antibody which has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (K_d) value of no more than about 1 x 10⁻⁷ M, preferably no more than about 1 x 10⁻⁸ and most preferably no more than about 1 x 10⁻⁹ M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

A "PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788,

PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptide" is an oligopeptide that binds, preferably specifically, to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as described herein. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptides usually are or are at least about 5 amino acids in length, alternatively are or are at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718,

PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as described herein. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 81:3998-4002 (1984); Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 82:178-182 (1985); Geysen et al., in Synthetic Peptides as Antigens, 130-149 (1986); Geysen et al., J. Immunol. Meth., 102:259-274 (1987); Schoofs et al., J. Immunol., 140:611-616 (1988), Cwirla, S. E. et al. (1990) Proc. Natl. Acad. Sci. USA, 87:6378; Lowman, H.B. et al. (1991) Biochemistry, 30:10832; Clackson, T. et al. (1991) Nature, 352: 624; Marks, J. D. et al. (1991), J. Mol. Biol., 222:581; Kang, A.S. et al. (1991) Proc. Natl. Acad. Sci. USA, 88:8363, and Smith, G. P. (1991) Current Opin. Biotechnol., 2:668).

A "PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecule" is an organic molecule other than an oligopeptide or antibody as defined herein that binds, preferably specifically, to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as described herein. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981,

PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules that are capable of binding, preferably specifically, to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585).

An antibody, oligopeptide or other organic molecule "which binds" an antigen of interest, e.g. a tumor-associated polypeptide antigen target, is one that binds the antigen with sufficient affinity such that the antibody, oligopeptide or other organic molecule is preferably useful as a diagnostic and/or therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. The extent of binding of the antibody, oligopeptide or other organic molecule to a "non-target" protein will be less than about 10% of the binding of the antibody, oligopeptide or other organic molecule to its particular target protein as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of an antibody, oligopeptide or other organic molecule to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term "specific binding" or "specifically binds to"

or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a K_d for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. The term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

An antibody, oligopeptide or other organic molecule that "inhibits the growth of tumor cells expressing a "PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250" or a "growth inhibitory" antibody, oligopeptide or other organic molecule is one which results in measurable growth inhibition of cancer cells expressing or overexpressing the appropriate PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferred growth inhibitory anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-

PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies, oligopeptides or organic molecules inhibit growth of PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-expressing tumor cells by or by greater than 20%, preferably from about 20% to about 50%, and even more preferably, by or by greater than 50% (e.g., from about 50% to about 100%) as compared to the appropriate control, the control typically being tumor cells not treated with the antibody, oligopeptide or other organic molecule being tested. Growth inhibition can be measured at an antibody concentration of about 0.1 to 30 µg/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. Growth inhibition of tumor cells *in vivo* can be determined in various ways. The antibody is growth inhibitory *in vivo* if administration of the anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody at about 1 µg/kg to about 100 mg/kg body weight results in reduction in tumor size or tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

An antibody, oligopeptide or other organic molecule which "induces apoptosis" is one which induces programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). The cell is usually one which overexpresses a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755,

PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Preferably the cell is a tumor cell, e.g., a prostate, breast, ovarian, stomach, endometrial, lung, kidney, colon, bladder cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody, oligopeptide or other organic molecule which induces apoptosis is one which results in or in about 2 to 50 fold, preferably in or in about 5 to 50 fold, and most preferably in or in about 10 to 50 fold, induction of annexin binding relative to untreated cell in an annexin binding assay.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

"Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in a animal model such as that disclosed in Clynes et al. Proc. Natl. Acad. Sci. U.S.A. 95:652-656 (1998).

"Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal

receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

"Human effector cells" are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least FcγRIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, e.g., from blood.

"Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996), may be performed.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD). Preferably, the cancer comprises a tumor that expresses an IGF receptor, more preferably breast cancer, lung cancer, colorectal cancer, or prostate cancer, and most preferably breast or prostate cancer.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas

such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e. g., calicheamicin, especially calicheamicin gammaII and calicheamicin omegaII (see, e.g., Agnew, *Chem Intl. Ed. Engl.*, 33: 183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, auranofin, azaserine, bleomycins, cactinomycin, 5 carabacin, carminomycin, carzinophilin, chromomycin, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites 10 such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitiostane, testolactone; anti- adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; 15 aceglutone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestabucil; bisantrene; edatrate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguanzone; mitoxantrone; mopidanmol; niraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2- ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiopeta; taxoids, e.g., TAXOL® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABAXANE™ Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American 25 Pharmaceutical Partners, Schaumburg, Illinois), and TAXOTERE® doxorubicin (Rhône- Poulenc Rorer, Antony, France); chlorambucil; GEMZAR® gemcitabine; 6- thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; 30 capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX® tamoxifen), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® toremifene; aromatase inhibitors that inhibit the enzyme 35 aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® megestrol acetate, AROMASIN® exemestane, formestane, fadrozole, RIVISOR® vorozole, FEMARA® letrozole, and ARIMIDEX® anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine

analog); antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC- α , Ralf and H-Ras; ribozymes such as a VEGF expression inhibitor (e.g., ANGIOZYME® ribozyme) and a HER2 expression inhibitor; vaccines such as gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; PROLEUKIN® rIL-2; LURTOTECAN® topoisomerase 1 inhibitor; ABARELIX® rrmRH; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are associated with some degree of abnormal cell proliferation. In one aspect of the invention, the cell proliferative disorder is cancer.

"Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

An antibody, oligopeptide or other organic molecule which "induces cell death" is one which causes a viable cell to become nonviable. The cell is one which expresses a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, preferably a cell that overexpresses a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as compared to a normal cell of the same tissue type. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferably, the cell is a cancer cell, e.g., a breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, thyroid, pancreatic or bladder cell. Cell death *in vitro* may be determined in the absence of complement and immune effector cells to distinguish cell death

induced by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, the assay for cell death may be performed using heat inactivated serum (i.e., in the absence of complement) and in the absence of immune effector cells. To determine whether the antibody, oligopeptide or other organic molecule is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue (see Moore et al. Cytotechnology 17:1-11 (1995)) or 7AAD can be assessed relative to untreated cells.

5 Preferred cell death-inducing antibodies, oligopeptides or other organic molecules are those which induce PI uptake in the PI uptake assay in BT474 cells.

As used herein, the term "immunoadhesion" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesion") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesions comprise a fusion of an amino acid sequence with the

10 desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesion part of an immunoadhesion molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesion may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or

15 IgM.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

"Replication-preventing agent" is an agent wherein replication, function, and/or growth of the cells is inhibited or prevented, or cells are destroyed, no matter what the mechanism, such as by apoptosis, angiostasis, cytosis, tumoricide, mytosis inhibition, blocking cell cycle progression, arresting cell growth, binding to tumors, acting as cellular mediators, etc. Such agents include a chemotherapeutic agent, cytotoxic agent, cytokine, growth-inhibitory agent, or anti-hormonal agent, e.g., an anti-estrogen compound such as tamoxifen, an

20 anti-progesterone such as onapristone (see, EP 616 812); or an anti-androgen such as flutamide, as well as aromatase inhibitors, or a hormonal agent such as an androgen.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., At^{211} , I^{131} , I^{125} , Y^{90} , Re^{186} , Re^{188} , Sm^{153} , Bi^{212} , P^{32} and radioactive isotopes of Lu), chemotherapeutic agents e.g. methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C,

30 chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor

35 cells.

Preferred cytotoxic agents herein for the specific tumor types to use in combination with the antagonists herein are as follows:

1. Prostate cancer: androgens, docetaxel, paclitaxel, estramustine, doxorubicin, mitoxantrone, antibodies to ErbB2

domain(s) such as 2C4 (WO 01/00245; hybridoma ATCC HB-12697), which binds to a region in the extracellular domain of ErbB2 (e.g., any one or more residues in the region from about residue 22 to about residue 584 of ErbB2, inclusive), AVASTIN™ anti-vascular endothelial growth factor (VEGF), TARCEVA™ OSI-774 (erlotinib) (Genenotech and OSI Pharmaceuticals), or other epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI's).

5 2. Stomach cancer: 5-fluorouracil (5FU), XELODA™ capecitabine, methotrexate, etoposide, cisplatin/carboplatin, paclitaxel, docetaxel, gemcitabine, doxorubicin, and CPT-11 (camptothecin-11; irinotecan, USA Brand Name: CAMPTOSAR®).

3. Pancreatic cancer: gemcitabine, 5FU, XELODA™ capecitabine, CPT-11, docetaxel, paclitaxel, cisplatin, carboplatin, TARCEVA™ erlotinib, and other EGFR TKI's.

10 4. Colorectal cancer: 5FU, XELODA™ capecitabine, CPT-11, oxaliplatin, AVASTIN™ anti-VEGF, TARCEVA™ erlotinib and other EGFR TKI's, and ERBITUX™ (formerly known as IMC-C225) human: murine-chimerized monoclonal antibody that binds to EGFR and blocks the ability of EGF to initiate receptor activation and signaling to the tumor.

15 5. Renal cancer: IL-2, interferon alpha, AVASTIN™ anti-VEGF, MEGACE™ (Megestrol acetate) progestin, vinblastine, TARCEVA™ erlotinib, and other EGFR TKI's.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially a PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-
 25 expressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent may be one which significantly reduces the percentage of PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-
 30 expressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine,

cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb).
5 Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

"Doxorubicin" is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

10 The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prolaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid
15 stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as
20 interferon - α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence
25 cytokines.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

30 The term "gene" refers to (a) a gene containing at least one of the DNA sequences disclosed herein; (b) any DNA sequence that encodes the amino acid sequence encoded by the DNA sequences disclosed herein and/or; ©) any DNA sequence that hybridizes to the complement of the coding sequences disclosed herein. Preferably, the term includes coding as well as noncoding regions, and preferably includes all sequences necessary for normal gene expression.

35 The term "gene targeting" refers to a type of homologous recombination that occurs when a fragment of genomic DNA is introduced into a mammalian cell and that fragment locates and recombines with endogenous homologous sequences. Gene targeting by homologous recombination employs recombinant DNA technologies to replace specific genomic sequences with exogenous DNA of particular design.

The term "homologous recombination" refers to the exchange of DNA fragments between two DNA

molecules or chromatids at the site of homologous nucleotide sequences.

The term "target gene" (alternatively referred to as "target gene sequence" or "target DNA sequence") refers to any nucleic acid molecule, polynucleotide, or gene to be modified by homologous recombination. The target sequence includes an intact gene, an exon or intron, a regulatory sequence or any region between genes. The target gene may comprise a portion of a particular gene or genetic locus in the individual's genomic DNA.

5 "Disruption" of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, 10 PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene occurs when a fragment of genomic DNA locates and recombines with an endogenous homologous sequence wherein the disruption is a deletion of the native gene or a portion thereof, or a mutation in the native gene or wherein the disruption is the functional inactivation of the native gene. 15 Alternatively, sequence disruptions may be generated by nonspecific insertional inactivation using a gene trap vector (i.e. non-human transgenic animals containing and expressing a randomly inserted transgene; see for example U.S. Pat. No. 6,436,707 issued August 20, 2002). These sequence disruptions or modifications may include insertions, missense, frameshift, deletion, or substitutions, or replacements of DNA sequence, or any combination thereof. Insertions include the insertion of entire genes, which may be of animal, plant, fungal, insect, 20 prokaryotic, or viral origin. Disruption, for example, can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal gene product's activity. Preferably, the disruption is a null disruption, wherein there is no significant expression of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene. 25

30 The term "native expression" refers to the expression of the full-length polypeptide encoded by the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene, at expression levels present in the wild-type mouse. Thus, a disruption in which there is "no 35

native expression" of the endogenous PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene refers to a partial or complete reduction of the expression of at least a portion of a polypeptide encoded by an endogenous PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene of a single cell, selected cells, or all of the cells of a mammal.

The term "knockout" refers to the disruption of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene wherein the disruption results in: the functional inactivation of the native gene; the deletion of the native gene or a portion thereof; or a mutation in the native gene.

The term "knock-in" refers to the replacement of the mouse ortholog (or other mouse gene) with a human cDNA encoding any of the specific human PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-encoding genes or variants thereof (ie. the disruption results in a replacement of a native mouse gene with a native human gene).

The term "construct" or "targeting construct" refers to an artificially assembled DNA segment to be

transferred into a target tissue, cell line or animal. Typically, the targeting construct will include a gene or a nucleic acid sequence of particular interest, a marker gene and appropriate control sequences. As provided herein, the targeting construct comprises a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 targeting construct. A "PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 targeting construct" includes a DNA sequence homologous to at least one portion of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene and is capable of producing a disruption in a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene in a host cell.

The term "transgenic cell" refers to a cell containing within its genome a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001,

PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene that has been disrupted, modified, altered, or replaced completely or partially by the method of gene targeting.

The term "transgenic animal" refers to an animal that contains within its genome a specific gene that has been disrupted or otherwise modified or mutated by the methods described herein or methods otherwise well known in the art. Preferably the non-human transgenic animal is a mammal. More preferably, the mammal is a rodent such as a rat or mouse. In addition, a "transgenic animal" may be a heterozygous animal (i.e., one defective allele and one wild-type allele) or a homozygous animal (i.e., two defective alleles). An embryo is considered to fall within the definition of an animal. The provision of an animal includes the provision of an embryo or foetus *in utero*, whether by mating or otherwise, and whether or not the embryo goes to term.

As used herein, the terms "selective marker" and "position selection marker" refer to a gene encoding a product that enables only the cells that carry the gene to survive and/or grow under certain conditions. For example, plant and animal cells that express the introduced neomycin resistance (Neo^r) gene are resistant to the compound G418. Cells that do not carry the Neo^r gene marker are killed by G418. Other positive selection markers are known to, or are within the purview of, those of ordinary skill in the art.

The term "modulates" or "modulation" as used herein refers to the decrease, inhibition, reduction, amelioration, increase or enhancement of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene function, expression, activity, or alternatively a phenotype associated with PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene.

The term "ameliorates" or "amelioration" as used herein refers to a decrease, reduction or elimination of a condition, disease, disorder, or phenotype, including an abnormality or symptom.

The term "abnormality" refers to any disease, disorder, condition, or phenotype in which PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925,

PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 is implicated, including pathological conditions and behavioral observations.

Table 1

```

/*
*
* C-C increased from 12 to 15
* Z is average of EQ
5  * B is average of ND
* match with stop is _M; stop-stop = 0; J (joker) match = 0
*/
#define _M      -8      /* value of a match with a stop */

10  int  _day[26][26] = {
/*  A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */  { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */  { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */  {-2, -4, 15, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
15  /* D */  { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */  { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */  {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */  { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */  {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
20  /* I */  {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */  {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */  {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */  {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
25  /* N */  { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */  {_M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */  { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */  { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */  {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
30  /* S */  { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */  { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */  { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */  {-6, -5, -8, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
35  /* X */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */  {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */  { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

40

45

50

```

Table 1 (cont')

```

/*
*/
#include <stdio.h>
#include <ctype.h>

5
#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
#define MX          4       /* save if there's at least MX-1 bases since last jmp */

10
#define DMAT         3      /* value of matching bases */
#define DMIS         0      /* penalty for mismatched bases */
#define DINS0        8      /* penalty for a gap */
#define DINS1        1      /* penalty per base */
15
#define PINS0        8      /* penalty for a gap */
#define PINS1        4      /* penalty per residue */

struct jmp {
20
    short            n[MAXJMP];    /* size of jmp (neg for dely) */
    unsigned short   x[MAXJMP];    /* base no. of jmp in seq x */
};                                /* limits seq to 2^16 -1 */

struct diag {
25
    int              score;         /* score at last jmp */
    long             offset;        /* offset of prev block */
    short            ijmp;          /* current jmp index */
    struct jmp        jp;           /* list of jmps */
};

30
struct path {
    int              spc;            /* number of leading spaces */
    short            n[JMPS];        /* size of jmp (gap) */
    int              x[JMPS];        /* loc of jmp (last elem before gap) */
};

35
char                *ofile;         /* output file name */
char                *namex[2];      /* seq names: getseqs() */
char                *prog;          /* prog name for err msgs */
char                *seqx[2];       /* seqs: getseqs() */
40
int                 dmax;           /* best diag: nw() */
int                 dmax0;          /* final diag */
int                 dna;            /* set if dna: main() */
int                 endgaps;        /* set if penalizing end gaps */
int                 gapx, gapy;     /* total gaps in seqs */
45
int                 len0, len1;     /* seq lens */
int                 ngapx, ngapy;   /* total size of gaps */
int                 smax;           /* max score: nw() */
int                 *xbm;           /* bitmap for matching */
long                offset;         /* current offset in jmp file */
50
struct diag         *dx;            /* holds diagonals */
struct path         pp[2];          /* holds path for seqs */

char                *calloc(), *malloc(), *index(), *strcpy();
char                *getseq(), *g_calloc();

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
5  * The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
* Output is in the file "align.out"
10 *
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
#include "nw.h"
15 #include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
20 };

static _pbval[26] = {
    1,2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
25 1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                main
{
    int      ac;
    char     *av[];
30
    prog = av[0];
    if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
40    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
45    xbm = (dna)? _dbval : _pbval;

    endgaps = 0;                /* 1 to penalize endgaps */
    ofile = "align.out";        /* output file */

50    nw();                      /* fill in the matrix, get the possible jumps */
    readjumps();                /* get the actual jumps */
    print();                    /* print stats, alignment */

    cleanup(0);                 /* unlink any tmp files */

```

Table 1 (cont')

```

/* do the alignment, return best score: main()
* dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
* pro: PAM 250 values
* When scores are equal, we prefer mismatches to any gap, prefer
5 * a new gap to extending an ongoing gap, and prefer a gap in seqx
* to a gap in seq y.
*/
nw()
{
10     char      *px, *py;          /* seqs and ptrs */
     int      *ndely, *dely;       /* keep track of dely */
     int      ndelx, delx;         /* keep track of delx */
     int      *tmp;               /* for swapping row0, row1 */
     int      mis;                /* score for each type */
15     int      ins0, ins1;         /* insertion penalties */
     register id;                 /* diagonal index */
     register ij;                 /* jmp index */
     register *col0, *col1;       /* score for curr, last row */
     register xx, yy;             /* index into seqs */
20
     dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));
     ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
     dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
     col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
25     col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
     ins0 = (dna)? DINS0 : PINS0;
     ins1 = (dna)? DINS1 : PINS1;
     smax = -10000;
     if (endgaps) {
30         for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
             col0[yy] = dely[yy] = col0[yy-1] - ins1;
             ndely[yy] = yy;
         }
         col0[0] = 0;             /* Waterman Bull Math Biol 84 */
35     }
     else
         for (yy = 1; yy <= len1; yy++)
             dely[yy] = -ins0;

/* fill in match matrix
40 */
     for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
         /* initialize first entry in col
         */
         if (endgaps) {
45             if (xx == 1)
                 col1[0] = delx = -(ins0+ins1);
             else
                 col1[0] = delx = col0[0] - ins1;
             ndelx = xx;
50         }
         else {
             col1[0] = 0;
             delx = -ins0;
             ndelx = 0;
55         }
     }

```

Table 1 (cont')

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
    * favor new del over ongoing del
    * ignore MAXGAP if weighting endgaps
    */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
    * favor new del over ongoing del
    */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
    * mis over any del and delx over dely
    */

    id = xx - yy + len1 - 1;
    if (mis >= delx && mis >= dely[yy])
        col1[yy] = mis;

```

...nw

Table 1 (cont')

```

5      else if (delx >= dely[yy]) {
        coll[yy] = delx;
        ij = dx[id].ijmp;
        if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
            dx[id].ijmp++;
            if (++ij >= MAXJMP) {
                writejms(id);
                ij = dx[id].ijmp = 0;
                dx[id].offset = offset;
                offset += sizeof(struct jmp) + sizeof(offset);
            }
            dx[id].jp.n[ij] = ndelx;
15      dx[id].jp.x[ij] = xx;
            dx[id].score = delx;
        }
        else {
20      coll[yy] = dely[yy];
            ij = dx[id].ijmp;
            if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
                && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                dx[id].ijmp++;
25      if (++ij >= MAXJMP) {
                    writejms(id);
                    ij = dx[id].ijmp = 0;
                    dx[id].offset = offset;
                    offset += sizeof(struct jmp) + sizeof(offset);
                }
30      dx[id].jp.n[ij] = -ndely[yy];
                dx[id].jp.x[ij] = xx;
                dx[id].score = dely[yy];
            }
35      if (xx == len0 && yy < len1) {
                /* last col
                */
                if (endgaps)
                    coll[yy] -= ins0+ins1*(len1-yy);
40      if (coll[yy] > smax) {
                    smax = coll[yy];
                    dmax = id;
                }
            }
45      }
            if (endgaps && xx < len0)
                coll[yy-1] -= ins0+ins1*(len0-xx);
            if (coll[yy-1] > smax) {
                smax = coll[yy-1];
50      dmax = id;
            }
        tmp = col0; col0 = coll; coll = tmp;
    }
    (void) free((char *)ndely);
    (void) free((char *)dely);
55  (void) free((char *)col0);
    (void) free((char *)coll);
}

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
5  * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line: dumpblock()
10 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

15 #include "nw.h"

#define SPC 3
#define P_LINE 256 /* maximum output line */
#define P_SPC 3 /* space between name or num and seq */

20 extern _day[26][26];
int olen; /* set output line length */
FILE *fx; /* output file */

25 print() print
{
    int lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
30         fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
35     olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
40         pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
45         lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
50     }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
55     getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

```

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
5  getmat(lx, ly, firstgap, lastgap)                                getmat
    int    lx, ly;                                /* "core" (minus endgaps) */
    int    firstgap, lastgap;                      /* leading trailing overlap */
{
    int    nm, i0, i1, siz0, siz1;
10    char    outx[32];
    double    pct;
    register    n0, n1;
    register char    *p0, *p1;
    /* get total matches, score
15    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
20    n1 = pp[0].spc + 1;
    nm = 0;
    while ( *p0 && *p1 ) {
        if (siz0) {
25            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
30            p0++;
            n0++;
            siz1--;
        }
        else {
35            if (xbm[*p0-'A'] & xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
40            p0++;
            p1++;
        }
    }

45    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
    if (endgaps)
50        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
    pct = 100.*(double)nm/(double)lx;
    fprintf(fx, "\n");
55    fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);

```


Table 1 (cont')

```

fprintf(fx, "<gaps in first sequence: %d", gapx);
if (gapx) {
    (void) sprintf(outx, " (%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? "" : "s");
5   fprintf(fx, "%s", outx);
    fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, " (%d %s%s)",
10      ngapy, (dna)? "base":"residue", (ngapy == 1)? "" : "s");
        fprintf(fx, "%s", outx);
    }
    if (dna)
        fprintf(fx,
15      "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
        smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
20      "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
        smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
25      "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
        firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
        lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
    else
        fprintf(fx, "<endgaps not penalized\n");
}
static      nm;          /* matches in core -- for checking */
static      lmax;        /* lengths of stripped file names */
30  static    ij[2];       /* jmp index for a path */
static      nc[2];        /* number at start of current line */
static      ni[2];        /* current elem number -- for gapping */
static      siz[2];
static char  *ps[2];       /* ptr to current element */
35  static char *po[2];     /* ptr to next output char slot */
static char  out[2][P_LINE]; /* output line */
static char  star[P_LINE]; /* set by stars */
/*
* print alignment of described in struct path pp[]
40  */
static
pr_align()
{
    int      nn;          /* char count */
45    int      more;
    register I;

    for (I = 0, lmax = 0; I < 2; I++) {
        nn = stripname(namex[i]);
50        if (nn > lmax)
            lmax = nn;
        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
55        ps[i] = seqx[i];
        po[i] = out[i];
    }

```

...getmat

pr_align

Table 1 (cont')

```

for (nn = nm = 0, more = 1; more; ) {
    for (I = more = 0; I < 2; I++) {
        /*
5         * do we have more of this sequence?
        */
        if (!*ps[i])
            continue;
        more++;
10        if (pp[i].spc) { /* leading space */
            *po[i]++ = ' ';
            pp[i].spc--;
        }
        else if (siz[i]) { /* in a gap */
15            *po[i]++ = '-';
            siz[i]--;
        }
        else { /* we're putting a seq element
                */
20            *po[i] = *ps[i];
            if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);
            po[i]++;
            ps[i]++;
25            /*
            * are we at next gap for this seq?
            */
            if (ni[i] == pp[i].x[ij[i]]) {
30                /*
                * we need to merge all gaps
                * at this location
                */
                siz[i] = pp[i].n[ij[i]++];
                while (ni[i] == pp[i].x[ij[i]])
35                    siz[i] += pp[i].n[ij[i]++];
            }
            ni[i]++;
        }
    }
40    if (++nn == olen || !more && nn) {
        dumpblock();
        for (I = 0; I < 2; I++)
            po[i] = out[i];
        nn = 0;
45    }
}

/*
 * dump a block of lines, including numbers, stars: pr_align()
50 */
static
dumpblock()
{
    register I;
55    for (I = 0; I < 2; I++)
        *po[i]-- = '\0';
}

```

...pr_align

dumpblock

Table 1 (cont')

...dumpblock

```

5      (void) putc('\n', fx);
      for (I = 0; I < 2; I++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (I == 0)
                  nums(I);
              if (I == 0 && *out[1])
                  stars();
              putline(I);
10         if (I == 0 && *out[1])
                fprintf(fx, star);
              if (I == 1)
                  nums(I);
          }
      }
15  }
      /*
      * put out a number line: dumpblock()
      */
20  static
      nums(ix)
      {
          int      ix;      /* index in out[] holding seq line */
          char      nline[P_LINE];
          register  I, j;
          register char *pn, *px, *py;
          for (pn = nline, I = 0; I < lmax+P_SPC; I++, pn++)
              *pn = ' ';
          for (I = nc[ix], py = out[ix]; *py; py++, pn++) {
30              if (*py == ' ' || *py == '-')
                  *pn = ' ';
              else {
                  if (I%10 == 0 || (I == 1 && nc[ix] != 1)) {
                      j = (I < 0)? -I : I;
                      for (px = pn; j; j /= 10, px--)
                          *px = j%10 + '0';
                      if (I < 0)
                          *px = '-';
35                  }
                  else
                      *pn = ' ';
                  I++;
              }
          }
45      *pn = '\0';
          nc[ix] = I;
          for (pn = nline; *pn; pn++)
              (void) putc(*pn, fx);
          (void) putc('\n', fx);
50  }
      /*
      * put out a line (name, [num], seq, [num]): dumpblock()
      */
      static
55  putline(ix)
      {
          int      ix;

```

nums

putline

Table 1 (cont')

...putline

```

int          I;
register char *px;

5   for (px = namex[ix], I = 0; *px && *px != '\0'; px++, I++)
      (void) putc(*px, fx);
      for (; I < lmax+P_SPC; I++)
          (void) putc(' ', fx);

10  /* these count from 1:
      * ni[] is current element (from 1)
      * nc[] is number at start of current line
      */
      for (px = out[ix]; *px; px++)
          (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
  }

20  /*
      * put a line of stars (seqs always in out[0], out[1]): dumpblock()
      */
      static
25  stars()
      {
          int          I;
          register char *p0, *p1, cx, *px;

30  if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
          !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
              return;
          px = star;
          for (I = lmax+P_SPC; I; I--)
35  *px++ = ' ';

          for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
              if (isalpha(*p0) && isalpha(*p1)) {
40  if (xbm[*p0-'A'] & xbm[*p1-'A']) {
                      cx = '*';
                      nm++;
                  }
                  else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
45  cx = '!';
                  else
                      cx = ' ';
              }
              else
50  cx = ' ';
              *px++ = cx;
          }
          *px++ = '\n';
          *px = '\0';
55  }

```

stars

Table 1 (cont')

```

/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
5 stripname(pn)
    char    *pn;    /* file name (may be path) */
{
    register char    *px, *py;
10     py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
15     if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}
20

```

stripname

Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
5  * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

10 char *jname = "/tmp/homgXXXXXX"; /* tmp file for jumps */
FILE *fj;
int cleanup(); /* cleanup tmp file */
long lseek();

15 /*
 * remove any tmp file if we blow
 */
cleanup(I)
20 {
    int I;

    if (fj)
        (void) unlink(jname);
    exit(I);
}
/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ',', '<', or '>'
 * seq in upper or lower case
 */
30 char *
getseq(file, len)
char *file; /* file name */
int *len; /* seq len */
{
35 char line[1024], *pseq;
register char *px, *py;
int natgc, tlen;
FILE *fp;
if ((fp = fopen(file, "r")) == 0) {
40     fprintf(stderr, "%s: can't read %s\n", prog, file);
    exit(1);
}
tlen = natgc = 0;
while (fgets(line, 1024, fp)) {
45     if (*line == ',' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++)
        if (isupper(*px) || islower(*px))
            tlen++;
50 }
if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
    fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
    exit(1);
}
55 pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

Table 1 (cont')

```

...getseq
    py = pseq + 4;
    *len = tlen;
    rewind(fp);
5    while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++) {
            if (isupper(*px))
10                *py++ = *px;
            else if (islower(*px))
                *py++ = toupper(*px);
            if (index("ATGCU", *(py-1)))
                natgc++;
15        }
    }
    *py++ = '\0';
    *py = '\0';
    (void) fclose(fp);
    dna = natgc > (tlen/3);
    return(pseq+4);
}
char *
20 g_alloc(msg, nx, sz)
    char *msg;          /* program, calling routine */
    int nx, sz;          /* number and size of elements */
{
    char *px, *calloc();
    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
30        if (*msg) {
            fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
35 }

/*
40 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
*/
readjmps()
{
    int fd = -1;
    int siz, i0, i1;
45    register I, j, xx;
    if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
            fprintf(stderr, "%s: can't open() %s\n", prog, jname);
50            cleanup(1);
        }
    }
    for (I = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; I++) {
        while (1) {
55            for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                ;

```

Table 1 (cont')

...readjumps

```

5         if (j < 0 && dx[dmax].offset && fj) {
            (void) lseek(fd, dx[dmax].offset, 0);
            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
            dx[dmax].ijmp = MAXJMP-1;
        }
        else
            break;
    }
    if (I >= JMPS) {
10         fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
    }
    if (j >= 0) {
15         siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
        if (siz < 0) { /* gap in second seq */
20             pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1 */
            pp[1].x[i1] = xx - dmax + len1 - 1;
            gapy++;
            ngapy -= siz;
            /* ignore MAXGAP when doing endgaps */
25             siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
            i1++;
        }
        else if (siz > 0) { /* gap in first seq */
30             pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
            gapx++;
            ngapx += siz;
            /* ignore MAXGAP when doing endgaps */
35             siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
            i0++;
        }
    }
    else
        break;
40 }
/* reverse the order of jumps */
for (j = 0, i0--, j < i0; j++, i0--) {
    I = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = I;
    I = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = I;
45 }
for (j = 0, i1--, j < i1; j++, i1--) {
    I = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = I;
    I = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = I;
50 }
if (fd >= 0)
    (void) close(fd);
if (fj) {
    (void) unlink(jname);
    fj = 0;
    offset = 0;
55 }

```


Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5  writejumps(ix)                                     writejumps
    int    ix;
    {
        char    *mktemp();
10         if (!fj) {
            if (mktemp(jname) < 0) {
                fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                cleanup(1);
            }
15         if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
20         (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
    }

```

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99

Table 2

PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXXXYYYYYY	(Length = 12 amino acids)

5 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

10 5 divided by 15 = 33.3%

Table 3

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

15

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

20

5 divided by 10 = 50%

Table 4

PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)

25

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

30

6 divided by 14 = 42.9%

Table 5

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLLVV	(Length = 9 nucleotides)

5 % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10 4 divided by 12 = 33.3%

II. Compositions and Methods of the Invention

A: Full-Length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides. In particular, cDNAs encoding various PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ

number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

B. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptide Variants

In addition to the full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides described herein, it is contemplated that PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,

PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variants can be prepared. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variants can be prepared by introducing appropriate nucleotide changes into the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 DNA, and/or by synthesis of the desired PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753,

PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or in various domains of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide that results in a change in the amino acid sequence of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as compared with the native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122,

PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide fragments share at least one biological and/or immunological activity with the native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide disclosed herein.

Conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated

exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are preferably introduced and the products screened.

Table 6

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

Substantial modifications in function or immunological identity of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the

charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

Amino acids may be grouped according to similarities in the properties of their side chains (in A. L. Lehninger, in *Biochemistry*, second ed., pp. 73-75, Worth Publishers, New York (1975)):

(1) non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M)

5 (2) uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q)

(3) acidic: Asp (D), Glu (E)

(4) basic: Lys (K), Arg (R), His(H)

Alternatively, naturally occurring residues may be divided into groups based on common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

10 (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

15 Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 variant DNA.

30 Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)].

35 If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptides

Covalent modifications of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436,

PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026,

PRO20110, PRO23203 or PRO35250 polypeptides (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 (for O-linked glycosylation sites). The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190,

PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides comprises linking the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618,

PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides of the present invention may also be modified in a way to form a chimeric molecule comprising the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide fused to another, heterologous polypeptide or amino acid sequence.

Such a chimeric molecule comprises a fusion of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755,

PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. The presence of such epitope-tagged forms of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., *Mol. Cell. Biol.*, 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., *Molecular and Cellular Biology*, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., *Protein Engineering*, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., *BioTechnology*, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., *Science*, 255:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., *J. Biol. Chem.*, 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., *Proc. Natl. Acad. Sci. USA*, 87:6393-6397 (1990)].

The chimeric molecule may comprise a fusion of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include

the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred aspect of the invention, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptides

The description below relates primarily to production of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides by culturing cells transformed or transfected with a vector containing PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295,

PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides. For instance, the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

1. Isolation of DNA Encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926,

PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptides

DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides may be obtained from a cDNA library prepared from tissue believed to possess the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 mRNA and to express it at a detectable level. Accordingly, human PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO69122, PRO204, PRO214, PRO222,

PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286,

PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935; PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203
5 or PRO35250 polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991)
10 and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for
15 prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van
20 Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae
30 such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product
35 fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which

has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

5 In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-,
10 PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250- encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others
15 include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and
20 *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]).
25 Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).
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Suitable host cells for the expression of glycosylated PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693,
35 PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides are derived from

multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-,

PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., *Proc. Natl. Acad. Sci. USA*, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., *Nature*, 282:39 (1979); Kingsman et al., *Gene*, 7:141 (1979); Tschemper et al., *Gene*, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, *Genetics*, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO69122-, PRO204-,

PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., *Nature*, 275:615 (1978); Goeddel et al., *Nature*, 281:544 (1979)], alkaline phosphatase, a tryptophan (trp) promoter system [Goeddel, *Nucleic Acids Res.*, 8:4057 (1980); EP 36,776], and hybrid promoters such as the tac promoter [deBoer et al., *Proc. Natl. Acad. Sci. USA*, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., *J. Biol. Chem.*, 255:2073 (1980)] or other glycolytic enzymes [Hess et al., *J. Adv. Enzyme Reg.*, 7:149 (1968); Holland, *Biochemistry*, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110,

PRO23203 or PRO35250 transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496,

PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-,

PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755,

PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher; Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide produced.

E. Uses for PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptides

Nucleotide sequences (or their complement) encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170,

PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 nucleic acid will also be useful for the preparation of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides by the recombinant techniques described herein.

1 0 The full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides or PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095,

PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides from other species) which have a desired sequence identity to the native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250. By way of example, a screening method will comprise isolating the coding region of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ^{32}P or ^{35}S , or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene of the present invention can be

used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 mRNA (sense) or PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO_4 -mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55

bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length, or more.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 coding sequences.

Nucleotide sequences encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can also be used to construct hybridization probes for mapping the gene which encodes that PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 encode a protein which binds to another protein (for example,

where the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 is a receptor), the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or a receptor for PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095,

PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. The invention provides cDNA encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide which can be used to clone genomic DNA encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573,

PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides. Any technique known in the art may be used to introduce a target gene transgene into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to pronuclear microinjection (U.S. Pat. Nos. 4,873,191, 4,736,866 and 4,870,009); retrovirus mediated gene transfer into germ lines (Van der Putten, et al., *Proc. Natl. Acad. Sci., USA*, 82:6148-6152 (1985)); gene targeting in embryonic stem cells (Thompson, et al., *Cell*, 56:313-321 (1989)); nonspecific insertional inactivation using a gene trap vector (U.S. Pat. No. 6,436,707); electroporation of embryos (Lo, *Mol. Cell. Biol.*, 3:1803-1814 (1983)); and sperm-mediated gene transfer (Lavitrano, et al., *Cell*, 57:717-723 (1989)); etc. Typically, particular cells would be targeted for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition. Alternatively, non-

human homologues of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides can be used to construct a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 "knock out" animal which has a defective or altered gene encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 proteins as a result of homologous recombination between the endogenous gene encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides and altered genomic DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides introduced into an embryonic stem cell of the animal. Preferably the knock out animal is a mammal. More

preferably, the mammal is a rodent such as a rat or mouse. For example, cDNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides can be used to clone genomic DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides in accordance with established techniques. A portion of the genomic DNA encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the gene encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316,

PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

5 In addition, knockout mice can be highly informative in the discovery of gene function and pharmaceutical utility for a drug target, as well as in the determination of the potential on-target side effects associated with a given target. Gene function and physiology are so well conserved between mice and humans, since they are both mammals and contain similar numbers of genes, which are highly conserved between the species. It has recently been well documented, for example, that 98% of genes on mouse chromosome 16 have
10 a human ortholog (Mural et al., Science 296:1661-71 (2002)).

Although gene targeting in embryonic stem (ES) cells has enabled the construction of mice with null mutations in many genes associated with human disease, not all genetic diseases are attributable to null mutations. One can design valuable mouse models of human diseases by establishing a method for gene replacement (knock-in) which will disrupt the mouse locus and introduce a human counterpart with mutation. Subsequently one can
15 conduct *in vivo* drug studies targeting the human protein (Kitamoto et. Al., Biochemical and Biophysical Res. Commun., 222:742-47 (1996)).

Nucleic acid encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434,
20 PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides may also be used in gene therapy. In gene therapy
25 applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has
30 already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik et al., Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques
35 vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically

retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau et al., Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes and the isolated nucleic acid sequences may be used for recombinantly expressing those markers.

The nucleic acid molecules encoding the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides described herein may also be employed as therapeutic agents. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981,

PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEENTM, PLURONICSTM or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In *Toxicokinetics and New Drug Development*, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434,

PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 µg/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, microencapsulation of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- (rhIFN-), interleukin-2, and MN rgp120. Johnson et al., Nat. Med., 2:795-799 (1996); Yasuda, Biomed. Ther., 27:1221-1223 (1993); Hora et al., Bio/Technology, 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine

Design: The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide (agonists) or prevent the effect of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide (antagonists). Agonists that mimic a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide would be especially valuable therapeutically in those instances where a negative phenotype is observed based on findings with the non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170,

PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Antagonists that prevent the effects of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide would be especially valuable therapeutically in those instances where a positive phenotype is observed based upon observations with the non-human transgenic knockout animal. Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptide with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,

PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-

protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be added to a cell along with the compound

to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide indicates that the compound is an antagonist to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Alternatively, antagonists may be detected by combining the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and a potential antagonist with membrane-bound PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718,

PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can be labeled, such as by radioactivity, such that the number of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475,

PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

Another approach in assessing the effect of an antagonist to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, would be administering a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 antagonist to a wild-type mouse in order to mimic a known knockout phenotype. Thus, one would initially knockout the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265,

PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene of interest and observe the resultant phenotype as a consequence of knocking out or disrupting the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene. Subsequently, one could then assess the effectiveness of an antagonist to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by administering an antagonist to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide to a wild-type mouse. An effective antagonist would be expected to mimic the phenotypic effect that was initially observed in the knockout animal.

Likewise, one could assess the effect of an agonist to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646,

PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, by administering a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 agonist to a non-human transgenic mouse in order to ameliorate a known negative knockout phenotype. Thus, one would initially knockout the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene of interest and observe the resultant phenotype as a consequence of knocking out or disrupting the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 gene. Subsequently, one could then assess the effectiveness of an agonist to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by administering an agonist to the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912,

PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide to a the non-human transgenic mouse. An effective agonist would be expected to ameliorate the negative phenotypic effect that was initially observed in the knockout animal.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with a labeled PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912,

PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

Another potential PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995,

PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, thereby blocking the normal biological activity of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it

promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

5 Diagnostic and therapeutic uses of the herein disclosed molecules may also be based upon the positive functional assay hits disclosed and described below.

F. Anti-PRO69122, Anti-PRO204, Anti-PRO214, Anti-PRO222, Anti-PRO234, Anti-PRO265, Anti-PRO309, Anti-PRO332, Anti-PRO342, Anti-PRO356, Anti-PRO540, Anti-PRO618, Anti-PRO944, Anti-PRO994, Anti-PRO1079, Anti-PRO1110, Anti-PRO1122, Anti-PRO1138, Anti-PRO1190, Anti-PRO1272, Anti-PRO1286, Anti-PRO1295, Anti-PRO1309, Anti-PRO1316, Anti-PRO1383, Anti-PRO1384, Anti-PRO1431, Anti-PRO1434, Anti-PRO1475, Anti-PRO1481, Anti-PRO1568, Anti-PRO1573, Anti-PRO1599, Anti-PRO1604, Anti-PRO1605, Anti-PRO1693, Anti-PRO1753, Anti-PRO1755, Anti-PRO1777, Anti-PRO1788, Anti-PRO1864, Anti-PRO1925, Anti-PRO1926, Anti-PRO3566, Anti-PRO4330, Anti-PRO4423, Anti-PRO36935, Anti-PRO4977, Anti-PRO4979, Anti-PRO4980, Anti-PRO4981, Anti-PRO5801, Anti-PRO5995, Anti-PRO6001, Anti-PRO6095, Anti-PRO6182, Anti-PRO7170, Anti-PRO7171, Anti-PRO7436, Anti-PRO9912, Anti-PRO9917, Anti-PRO37337, Anti-PRO37496, Anti-PRO19646, Anti-PRO21718, Anti-PRO19820, Anti-PRO21201, Anti-PRO20026, Anti-PRO20110, Anti-PRO23203 or Anti-PRO35250 Antibodies

The present invention provides anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies which may find use herein as therapeutic and/or diagnostic agents.

Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (especially when synthetic peptides are used) to a protein that is immunogenic in the species to be immunized. For example, the antigen can be conjugated to keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, e.g., maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues),

glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

2. Monoclonal Antibodies

Monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 and derivatives e.g., X63-Ag8-653 cells available from the American Type Culture Collection, Manassas, Virginia, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson et al., Anal. Biochem., 107:220 (1980).

Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal e.g., by i.p. injection of the cells into mice.

5 The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (e.g., using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, etc.

10 DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles
15 on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., Curr. Opinion in Immunol., 5:256-262 (1993) and Plückthun, Immunol. Revs. 130:151-188 (1992).

Monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990). Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991) describe the isolation of murine and human
20 antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., Nuc. Acids. Res. 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

25 The DNA that encodes the antibody may be modified to produce chimeric or fusion antibody polypeptides, for example, by substituting human heavy chain and light chain constant domain (C_H and C_L) sequences for the homologous murine sequences (U.S. Patent No. 4,816,567; and Morrison, et al., Proc. Natl Acad. Sci. USA, 81:6851 (1984)), or by fusing the immunoglobulin coding sequence with all or part of the coding sequence for a non-immunoglobulin polypeptide (heterologous polypeptide). The non-immunoglobulin
30 polypeptide sequences can substitute for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

35 3. Human and Humanized Antibodies

The anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-

PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeven et al., *Science*, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity and HAMA response (human anti-mouse antibody) when the antibody is intended for human therapeutic use. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody (Sims et al., *J. Immunol.* 151:2296 (1993);

Chothia et al., J. Mol. Biol., 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high binding affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

Various forms of a humanized anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody are contemplated. For example, the humanized antibody may be an antibody fragment, such as a Fab, which is optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized antibody may be an intact antibody, such as an intact IgG1 antibody.

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno. 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); 5,545,807; and WO 97/17852.

Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 [1990]) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, reviewed in, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or Griffith et al., EMBO J. 12:725-734 (1993). See, also, U.S. Patent Nos. 5,565,332 and 5,573,905.

As discussed above, human antibodies may also be generated by *in vitro* activated B cells (see U.S. Patents 5,567,610 and 5,229,275).

4. Antibody fragments

In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to solid tumors.

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical Methods 24:107-117 (1992); and Brennan et al., Science, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter et al., Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')₂ fragment with increased *in vivo* half-life comprising a salvage receptor binding epitope residues are described in U.S. Patent No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. The antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894; and U.S. Patent No. 5,587,458. Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during *in vivo* use. sFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. See Antibody Engineering, ed. Borrebaeck, supra. The antibody fragment may also be a "linear antibody", e.g., as described in U.S. Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

5. Bispecific Antibodies

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 protein as described herein. Other such antibodies may combine a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 binding site with a binding site for another protein. Alternatively, an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD3), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), so as to focus and localize cellular defense mechanisms to the PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-expressing cell. Bispecific antibodies may also

be used to localize cytotoxic agents to cells which express a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide. These antibodies possess a PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-binding arm and an arm which binds the cytotoxic agent (e.g., saporin, anti-interferon- α , vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., F(ab')₂ bispecific antibodies).

WO 96/16673 describes a bispecific anti-ErbB2/anti-Fc γ RIII antibody and U.S. Patent No. 5,837,234 discloses a bispecific anti-ErbB2/anti-Fc γ RI antibody. A bispecific anti-ErbB2/Fc α antibody is shown in WO98/02463. U.S. Patent No. 5,821,337 teaches a bispecific anti-ErbB2/anti-CD3 antibody.

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., *Nature* 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., *EMBO J.* 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificity (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. Preferably, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three

polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant affect on the yield of the desired chain combination.

The invention provides bispecific antibodies which are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology 121:210 (1986).

According to another approach described in U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent, sodium arsenite, to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets. Various

techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a V_H connected to a V_L by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., J. Immunol., 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., J. Immunol. 147:60 (1991).

6. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

7. Multivalent Antibodies

A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of the present invention can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (e.g. tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. The preferred dimerization domain comprises (or consists of) an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. The preferred multivalent antibody herein comprises (or consists of) three to about eight, but preferably four, antigen binding sites. The multivalent antibody comprises at least one polypeptide chain (and preferably two polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the polypeptide chain(s) may comprise VD1-(X1)_n-VD2-(X2)_n-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: VH-CH1-flexible linker-VH-

CH1-Fc region chain; or VH-CH1-VH-CH1-Fc region chain. The multivalent antibody herein preferably further comprises at least two (and preferably four) light chain variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain.

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8. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, e.g., so as to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., *J. Exp. Med.* 176:1191-1195 (1992) and Shopes, B. *J. Immunol.* 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al., *Cancer Research* 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., *Anti-Cancer Drug Design* 3:219-230 (1989). To increase the serum half life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG₁, IgG₂, IgG₃, or IgG₄) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

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9. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, a growth inhibitory agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

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Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcumin, croton, saponaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ²¹²Bi, ¹³¹I, ¹³¹In, ⁹⁰Y, and ¹⁸⁶Re. Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-

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active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminopentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

Conjugates of an antibody and one or more small molecule toxins, such as a calicheamicin, maytansinoids, a trichothene, and CC1065, and the derivatives of these toxins that have toxin activity, are also contemplated herein.

Maytansine and maytansinoids

The invention provides an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody (full length or fragments) which is conjugated to one or more maytansinoid molecules.

Maytansinoids are mitototic inhibitors which act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Patent No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Patent No. 4,151,042). Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Patent Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533, the disclosures of which are hereby expressly incorporated by reference.

Maytansinoid-antibody conjugates

In an attempt to improve their therapeutic index, maytansine and maytansinoids have been conjugated to antibodies specifically binding to tumor cell antigens. Immunoconjugates containing maytansinoids and their therapeutic use are disclosed, for example, in U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1, the disclosures of which are hereby expressly incorporated by reference. Liu *et al.*, Proc. Natl. Acad. Sci. USA **93**:8618-8623 (1996) described immunoconjugates comprising a maytansinoid designated DM1 linked to the monoclonal antibody C242 directed against human colorectal cancer. The conjugate was found to be highly cytotoxic towards cultured colon cancer cells, and showed antitumor activity in an *in vivo* tumor growth assay. Chari *et al.*, Cancer Research **52**:127-131 (1992) describe immunoconjugates in which a maytansinoid was conjugated via a disulfide linker to the murine antibody A7 binding to an antigen on human colon cancer cell lines,

or to another murine monoclonal antibody TA.1 that binds the HER-2/*neu* oncogene. The cytotoxicity of the TA.1-maytansinoid conjugate was tested *in vitro* on the human breast cancer cell line SK-BR-3, which expresses 3×10^5 HER-2 surface antigens per cell. The drug conjugate achieved a degree of cytotoxicity similar to the free maytansinoid drug, which could be increased by increasing the number of maytansinoid molecules per antibody molecule. The A7-maytansinoid conjugate showed low systemic cytotoxicity in mice.

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Anti-PRO69122, Anti-PRO204, Anti-PRO214, Anti-PRO222, Anti-PRO234, Anti-PRO265, Anti-PRO309, Anti-PRO332, Anti-PRO342, Anti-PRO356, Anti-PRO540, Anti-PRO618, Anti-PRO944, Anti-PRO994, Anti-PRO1079, Anti-PRO1110, Anti-PRO1122, Anti-PRO1138, Anti-PRO1190, Anti-PRO1272, Anti-PRO1286, Anti-PRO1295, Anti-PRO1309, Anti-PRO1316, Anti-PRO1383, Anti-PRO1384, Anti-PRO1431, Anti-PRO1434, Anti-PRO1475, Anti-PRO1481, Anti-PRO1568, Anti-PRO1573, Anti-PRO1599, Anti-PRO1604, Anti-PRO1605, Anti-PRO1693, Anti-PRO1753, Anti-PRO1755, Anti-PRO1777, Anti-PRO1788, Anti-PRO1864, Anti-PRO1925, Anti-PRO1926, Anti-PRO3566, Anti-PRO4330, Anti-PRO4423, Anti-PRO36935, Anti-PRO4977, Anti-PRO4979, Anti-PRO4980, Anti-PRO4981, Anti-PRO5801, Anti-PRO5995, Anti-PRO6001, Anti-PRO6095, Anti-PRO6182, Anti-PRO7170, Anti-PRO7171, Anti-PRO7436, Anti-PRO9912, Anti-PRO9917, Anti-PRO37337, Anti-PRO37496, Anti-PRO19646, Anti-PRO21718, Anti-PRO19820, Anti-PRO21201, Anti-PRO20026, Anti-PRO20110, Anti-PRO23203 or Anti-PRO35250 Antibody-Maytansinoid Conjugates (Immunoconjugates)

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Anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody-maytansinoid conjugates are prepared by chemically linking an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the

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maytansinoid molecule. An average of 3-4 maytansinoid molecules conjugated per antibody molecule has shown efficacy in enhancing cytotoxicity of target cells without negatively affecting the function or solubility of the antibody, although even one molecule of toxin/antibody would be expected to enhance cytotoxicity over the use of naked antibody. Maytansinoids are well known in the art and can be synthesized by known techniques or isolated from natural sources. Suitable maytansinoids are disclosed, for example, in U.S. Patent No. 5,208,020 and in the other patents and nonpatent publications referred to hereinabove. Preferred maytansinoids are maytansinol and maytansinol analogues modified in the aromatic ring or at other positions of the maytansinol molecule, such as various maytansinol esters.

There are many linking groups known in the art for making antibody-maytansinoid conjugates, including, for example, those disclosed in U.S. Patent No. 5,208,020 or EP Patent 0 425 235 B1, and Chari et al., Cancer Research 52:127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

Conjugates of the antibody and maytansinoid may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Particularly preferred coupling agents include N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) (Carlsson et al., Biochem. J. 173:723-737 [1978]) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) to provide for a disulfide linkage.

The linker may be attached to the maytansinoid molecule at various positions, depending on the type of the link. For example, an ester linkage may be formed by reaction with a hydroxyl group using conventional coupling techniques. The reaction may occur at the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with a hydroxyl group, and the C-20 position having a hydroxyl group. The linkage is formed at the C-3 position of maytansinol or a maytansinol analogue.

Calicheamicin

Another immunoconjugate of interest comprises an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201,

anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see U.S. patents 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to, γ_1^I , α_2^I , α_3^I , N-acetyl- γ_1^I , PSAG and θ_1^I (Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. patents to American Cyanamid). Another anti-tumor drug that the antibody can be conjugated is QFA which is an antifolate. Both calicheamicin and QFA have intracellular sites of action and do not readily cross the plasma membrane. Therefore, cellular uptake of these agents through antibody mediated internalization greatly enhances their cytotoxic effects.

Other cytotoxic agents

Other antitumor agents that can be conjugated to the anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies of the invention include BCNU, streptozocin, vincristine and 5-fluorouracil, the family of agents known collectively LL-E33288 complex described in U.S. patents 5,053,394, 5,770,710, as well as esperamicins (U.S. patent 5,877,296).

Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, croton, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232 published October 28, 1993.

The present invention further contemplates an immunoconjugate formed between an antibody and a compound with nucleolytic activity (e.g., a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

For selective destruction of the tumor, the antibody may comprise a highly radioactive atom. A variety of radioactive isotopes are available for the production of radioconjugated anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-

PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. When the conjugate is used for diagnosis, it may comprise a radioactive atom for scintigraphic studies, for example tc^{99m} or I¹²³, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

The radio- or other labels may be incorporated in the conjugate in known ways. For example, the peptide may be biosynthesized or may be synthesized by chemical amino acid synthesis using suitable amino acid precursors involving, for example, fluorine-19 in place of hydrogen. Labels such as tc^{99m} or I¹²³, Re¹⁸⁶, Re¹⁸⁸ and In¹¹¹ can be attached via a cysteine residue in the peptide. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker et al (1978) Biochem. Biophys. Res. Commun. 80: 49-57 can be used to incorporate iodine-123. "Monoclonal Antibodies in Immunoscintigraphy" (Chatal, CRC Press 1989) describes other methods in detail.

Conjugates of the antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., Cancer Research 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

Alternatively, a fusion protein comprising the anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-

PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody and cytotoxic agent may be made, e.g., by recombinant techniques or peptide synthesis. The length of DNA may comprise respective regions encoding the two portions of the conjugate either adjacent one another or separated by a region encoding a linker peptide which does not destroy the desired properties of the conjugate.

The invention provides that the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pre-targeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

10. Immunoliposomes

The anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies disclosed herein may also be formulated as immunoliposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030 (1980); U.S. Pat. Nos. 4,485,045 and 4,544,545; and WO97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem. 257:286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al., J. National Cancer Inst. 81(19):1484 (1989).

11. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the

form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

G. Uses for Anti-PRO69122, Anti-PRO204, Anti-PRO214, Anti-PRO222, Anti-PRO234, Anti-PRO265, Anti-PRO309, Anti-PRO332, Anti-PRO342, Anti-PRO356, Anti-PRO540, Anti-PRO618, Anti-PRO944, Anti-PRO994, Anti-PRO1079, Anti-PRO1110, Anti-PRO1122, Anti-PRO1138, Anti-PRO1190, Anti-PRO1272, Anti-PRO1286, Anti-PRO1295, Anti-PRO1309, Anti-PRO1316, Anti-PRO1383, Anti-PRO1384, Anti-PRO1431, Anti-PRO1434, Anti-PRO1475, Anti-PRO1481, Anti-PRO1568, Anti-PRO1573, Anti-PRO1599, Anti-PRO1604, Anti-PRO1605, Anti-PRO1693, Anti-PRO1753, Anti-PRO1755, Anti-PRO1777, Anti-PRO1788, Anti-PRO1864, Anti-PRO1925, Anti-PRO1926, Anti-PRO3566, Anti-PRO4330, Anti-PRO4423, Anti-PRO36935, Anti-PRO4977, Anti-PRO4979, Anti-PRO4980, Anti-PRO4981, Anti-PRO5801, Anti-PRO5995, Anti-PRO6001, Anti-PRO6095, Anti-PRO6182, Anti-PRO7170, Anti-PRO7171, Anti-PRO7436, Anti-PRO9912, Anti-PRO9917, Anti-PRO37337, Anti-PRO37496, Anti-PRO19646, Anti-PRO21718, Anti-PRO19820, Anti-PRO21201, Anti-PRO20026, Anti-PRO20110, Anti-PRO23203 or Anti-PRO35250 Antibodies

The anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies of the invention have various therapeutic and/or diagnostic utilities for a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an immunological disorder; an oncological disorder, an embryonic developmental disorder or lethality, or a metabolic abnormality. For example, anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342,

anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies may be used in diagnostic assays for PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250, e.g., detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies also are useful for the affinity purification of PRO69122, PRO204, PRO214,

PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides from recombinant cell culture or natural sources. In this process, the antibodies against PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides are immobilized on a suitable support, such as a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095,

PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide from the antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

5 All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

10 Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

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The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

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Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

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Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel *et al.*, Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

30

35

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo

dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; *see*, Holmes *et al.*, Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

5 EXAMPLE 2: Isolation of cDNA clones by Amylase Screening

1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linked cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

2. Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linked with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, *e.g.* CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL⁺, SUC⁺, GAL⁺. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*,

sec62, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

5 Transformation was performed based on the protocol outlined by Gietz *et al.*, Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2×10^6 cells/ml (approx. $OD_{600}=0.1$) into fresh YEPD broth (500 ml) and regrown to 1×10^7 cells/ml (approx. $OD_{600}=0.4-0.5$).

10 The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li_2OOCCH_3), and resuspended into LiAc/TE (2.5 ml).

15 Transformation took place by mixing the prepared cells (100 μ l) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 μ g, vol. < 10 μ l) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 μ l, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li_2OOCCH_3 , pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes; and
20 the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 μ l, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 μ l) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

25 Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

30 The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely *et al.*, Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

35 The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 μ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 μ l) was used as a template for the PCR reaction in a 25 μ l volume containing: 0.5 μ l KlenTaq (Clontech, Palo Alto, CA); 4.0 μ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 μ l KlenTaq buffer (Clontech); 0.25 μ l forward oligo 1; 0.25 μ l reverse oligo 2; 12.5 μ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACGACGCGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:143)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:144)

PCR was then performed as follows:

a.	Denature	92°C, 5 minutes
b.	3 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	59°C, 30 seconds
	Extend	72°C, 60 seconds
c.	3 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	57°C, 30 seconds
	Extend	72°C, 60 seconds
d.	25 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	55°C, 30 seconds
	Extend	72°C, 60 seconds
e.	Hold	4°C

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 μ l) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook *et al.*, *supra*. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (*e.g.*, GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first

ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below. In addition, the sequence of DNA284870 encoding PRO69122 polypeptides was identified from GenBank accession no.: AF052059; the sequence of DNA38649 encoding PRO342 polypeptides was identified from GenBank accession no.: AY358342; the sequence of DNA336539 encoding PRO36935 polypeptides was identified from GenBank accession no.: Z29083 the sequence of DNA222844 encoding PRO4979 polypeptides (also known as PRO38844 polypeptides) was identified from GenBank accession no.: AB098597; the sequence of DNA98380 encoding PRO6001 polypeptides was identified from GenBank accession no.: AY358785; the sequence of DNA226874 encoding PRO37337 polypeptides was identified from GenBank accession no.: Y07909; the sequence of DNA227033 encoding PRO37496 polypeptides was identified from GenBank accession no.: BC003006; and the sequence of DNA188342 encoding PRO21718 polypeptides was identified from GenBank accession no.: AF146761.

Table 7

	<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
	DNA30871-1157	209380	October 16, 1997
	DNA32286-1191	209385	October 16, 1997
30	DNA33107-1135	209251	September 16, 1997
	DNA35557-1137	209255	September 16, 1998
	DNA36350-1158	209378	October 16, 1997
	DNA61601-1223	209713	March 31, 1998
	DNA40982-1235	209433	November 7, 1997
35	DNA47470-1130P1	209422	October 28, 1997
	DNA44189-1322	209699	March 26, 1998
	DNA49152-1324	209813	April 28, 1998
	DNA52185-1370	209861	May 14, 1998

	DNA58855-1422	203018	June 23, 1998
	DNA56050-1455	203011	June 23, 1998
	DNA58727-1474	203171	September 1, 1998
	DNA62377-1381-1	203552	December 22, 1998
	DNA58850-1495	209956	June 9, 1998
5	DNA59586-1520	203288	September 29, 1998
	DNA64896-1539	203238	September 9, 1998
	DNA64903-1553	203223	September 15, 1998
	DNA59218-1559	203287	September 29, 1998
	DNA59588-1571	203106	August 11, 1998
10	DNA60608-1577	203126	August 18, 1998
	DNA58743-1609	203154	August 25, 1998
	DNA71159-1617	203135	August 18, 1998
	DNA73401-1633	203273	September 22, 1998
	DNA68818-2536	203657	February 9, 1999
15	DNA61185-1646	203464	November 17, 1998
	DNA58732-1650	203290	September 29, 1998
	DNA68880-1676	203319	October 6, 1998
	DNA73735-1681	203356	October 20, 1998
	DNA62845-1684	203361	October 20, 1998
20	DNA71286-1687	203357	October 20, 1998
	DNA77648-1688	203408	October 27, 1998
	DNA77301-1708	203407	October 27, 1998
	DNA68883-1691	203535	December 15, 1998
	DNA76396-1698	203471	November 17, 1998
25	DNA77652-2505	203480	November 17, 1998
	DNA71235-1706	203584	January 12, 1999
	DNA45409-2511	203579	January 12, 1999
	DNA82302-2529	203534	December 15, 1998
	DNA82340-2530	203547	December 22, 1998
30	DNA59844-2542	203650	February 9, 1999
	DNA90842-2574	203845	March 16, 1999
	DNA96893-2621	PTA-12	May 4, 1999
	DNA62849-2647	PTA-205	June 8, 1999
	DNA97003-2649	PTA-43	May 11, 1999
35	DNA94849-2960	PTA-2306	July 25, 2000
	DNA115291-2681	PTA-202	June 8, 1999
	DNA96988-2685	PTA-384	July 20, 1999
	DNA105680-2710	PTA-483	August 3, 1999

	DNA110700-2716	PTA-512	August 10, 1999
	DNA108722-2743	PTA-552	August 17, 1999
	DNA108670-2744	PTA-546	August 17, 1999
	DNA119535-2756	PTA-613	August 31, 1999
	DNA108700-2802	PTA-1093	December 22, 1999
5	DNA119474-2803	PTA-1097	December 22, 1999
	DNA145841-2868	PTA-1678	April 11, 2000
	DNA149911-2885	PTA-1776	April 25, 2000
	DNA168028-2956	PTA-2304	July 25, 2000
	DNA154095-2998	PTA-2591	October 10, 2000
10	DNA185171-2994	PTA-2513	September 26, 2000
	DNA171732-3100	PTA-3329	April 24, 2001

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO204 Polypeptides [UNQ178]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified. Human fetal retina cDNA libraries were screened with PCR oligonucleotide primers and confirmed by hybridization with synthetic oligonucleotide probe which was based upon the EST sequence.

hybridization probe:

5'-GGCATGCAGCAGCTGGACATTTGCGAGGGCTTTTGCTGGCTG-3' (SEQ ID NO:145)

forward PCR primer:

5'-CTGCTGCAGAGTTGCACGAAC-3' (SEQ ID NO:146)

reverse PCR primer 1:

5'-CAGTTGTTGTTGTTCACAGAGAAG-3' (SEQ ID NO:147)

reverse PCR primer 2:

5'-AGTTCGTGCAACTCTGCAGCAG-3'

(SEQ ID NO:148)

A cDNA clone was identified and sequenced in entirety. The entire nucleotide sequence of the identified clone DNA3087-1157 is shown in Figure 3 (SEQ ID NO:3). Clone DNA30871-1157 (SEQ ID NO:3) contains a single open reading frame with an apparent translation initiation site at nucleotide positions 376-378 and ending at the stop codon (TAA) found at nucleotide positions 1498-1500 (Figure 3; SEQ ID NO:3), as indicated by bolded underline. The predicted PRO204 polypeptide precursor (i.e., UNQ178, SEQ ID NO:4) is 374 amino acids long, has a calculated molecular weight of 39,285 daltons, a pI of 6.06 and is shown in Figure 4. A cDNA containing DNA encoding UNQ178 (SEQ ID NO:3) has been deposited with the ATTC on October 16, 1997 and has been assigned deposit number 209380.

EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO214 Polypeptides [UNQ188]

A consensus DNA sequence was assembled using phrap as described in Example 1 above. This consensus DNA sequence is designated herein as DNA28744. Based on this consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence.

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified below. A positive library was then used to isolate clones encoding the PRO214 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal lung tissue.

A cDNA clone was sequenced in its entirety. The full length nucleotide sequence of DNA32286-1191 is shown in Figure 5 (SEQ ID NO:5). DNA32286-1191 contains a single open reading frame with an apparent translational initiation site at nucleotide position 103 (Fig. 5; SEQ ID NO:5). The predicted polypeptide precursor is 420 amino acids long (Fig. 6; SEQ ID NO:6).

Based on a BLAST and FastA sequence alignment analysis of the full-length sequence, PRO214 polypeptide shows amino acid sequence identity to HT protein and/or Fibulin (49% and 38%, respectively).

The oligonucleotide sequences used in the above procedure were the following:

28744.p (OLI555)

5'-CCTGGCTATCAGCAGGTGGGCTCCAAGTGTCTCGATGTGGATGAGTGTGA-3' (SEQ ID NO:149)

28744.f (OLI556)

5'-ATTCTGCGTGAACTGAGGGC-3' (SEQ ID NO:150)

28744.r (OLI557)

5'-ATCTGCTTGTAGCCCTCGGCAC-3' (SEQ ID NO:151)

EXAMPLE 6: Isolation of cDNA clones Encoding Human PRO222 Polypeptides [UNQ196]

A consensus DNA sequence was assembled relative to the other identified EST sequences as described in Example 1 above, wherein the consensus sequence is designated herein as DNA28771. Based on the DNA28771 consensus sequence, oligonucleotides were synthesized to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for

PRO222.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-ATCTCCTATCGCTGCTTTCCCGG-3' (SEQ ID NO:152)

reverse PCR primer 5'-AGCCAGGATCGCAGTAAACTCC-3' (SEQ ID NO:153)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA28771 sequence which had the following nucleotide sequence:

hybridization probe

5'-ATTTAAACTTGATGGGTCTGCGTATCTTGAGTGCTTACAAAACCTTATCT-3' (SEQ ID NO:154)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO222 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO222 [herein designated as DNA33107-1135] and the derived protein sequence for PRO222.

The entire nucleotide sequence of DNA33107-1135 is shown in Figure 7 (SEQ ID NO:7). Clone DNA33107-1135 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 159-161 and ending at the stop codon at nucleotide positions 1629-1631 (Fig. 7; SEQ ID NO:7). The predicted polypeptide precursor is 490 amino acids long (Fig. 8; SEQ ID NO:8). Clone DNA33107-1135 has been deposited with ATCC on September 16, 1997 and is assigned ATCC deposit no. ATCC 209251.

Based on a BLAST and FastA sequence alignment analysis of the full-length sequence, PRO222 shows amino acid sequence identity to mouse complement factor h precursor (25-26%), complement receptor (27-29%), mouse complement C3b receptor type 2 long form precursor (25-47%) and human hypothetical protein kiaa0247 (40%).

EXAMPLE 7: Isolation of cDNA clones Encoding Human PRO234 Polypeptides [UNQ208]

A consensus DNA sequence was assembled (DNA30926) using phrap as described in Example 1 above. Based on this consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence.

RNA for the construction of the cDNA libraries was isolated using standard isolation protocols, e.g., Ausubel et al., Current Protocols in Molecular Biology, from tissue or cell line sources or it was purchased from commercial sources (e.g., Clontech). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods (e.g., Ausubel et al.) using commercially available reagents (e.g., Invitrogen). This library was derived from 22 week old fetal brain tissue.

A cDNA clone was sequenced in its entirety and is herein designated DNA35557-1137 (SEQ ID NO:9). The entire nucleotide sequence of DNA35557-1137 is shown in Figure 9 (SEQ ID NO:9). The predicted polypeptide precursor is 382 amino acids long (designated PRO234; SEQ ID NO:10; FIGURE 10) and has a calculated molecular weight of approximately 43.1 kDa.

The oligonucleotide sequences used in the above procedure were the following:

30926.p (OLI826) (SEQ ID NO:155):

5'-GTTTCATTGAAAACCTCTTGCCATCT GATGGTGACTTCTGGATTGGGCTCA-3'

30926.f (OLI827) (SEQ ID NO:156):

5'-AAGCCAAAGAAGCCTGCAGGAGGG-3'

30926.r (OLI828) (SEQ ID NO:157):

5'-CAGTCCAAGCATAAAGGTCCTGGC-3'

5

EXAMPLE 8: Isolation of cDNA clones Encoding Human PRO265 Polypeptides [UNO232]

A consensus DNA sequence was assembled relative to other EST sequences as described in Example 1 above using phrap. This consensus sequence is herein designated DNA33679. Based on the DNA33679 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO265.

10

PCR primers (two forward and one reverse) were synthesized:

forward PCR primer A: 5'-CGGTCTACCTGTATGGCAACC-3' (SEQ ID NO:158);

forward PCR primer B: 5'-GCAGGACAACCAGATAAACCAC-3' (SEQ ID NO:159);

reverse PCR primer 5'-ACGCAGATTTGAGAAGGCTGTC-3' (SEQ ID NO:160)

15

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA33679 sequence which had the following nucleotide sequence

hybridization probe

5'-TTCACGGGCTGCTCTTGCCCAGCTCTTGAAGCTTGAAGAGCTGCAC-3' (SEQ ID NO:161)

20

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO265 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human a fetal brain library.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO265 [herein designated as DNA36350-1158] (SEQ ID NO:11) and the derived protein sequence for PRO265.

25

The entire nucleotide sequence of DNA36350-1158 is shown in Figure 11 (SEQ ID NO:11). Clone DNA36350-1158 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 352-354 and ending at the stop codon at positions 2332-2334 (Figure 11). The predicted polypeptide precursor is 660 amino acids long (Figure 12; SEQ ID NO:12). Clone DNA36350-1158 has been deposited with ATCC on October 16, 1997 and is assigned ATCC deposit no. ATCC 209378.

30

Analysis of the amino acid sequence of the full-length PRO265 polypeptide suggests that portions of it possess significant homology to the fibromodulin and the fibromodulin precursor, thereby indicating that PRO265 may be a novel member of the leucine rich repeat family, particularly related to fibromodulin.

EXAMPLE 9: Isolation of cDNA clones Encoding Human PRO309 Polypeptides [UNO272]

35

An expressed sequence tag (EST) DNA database (LIFESEQTM, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which was in a fetal pancreas library which shared significant identity which the adaptor protein Shc. A full length cDNA corresponding to the isolated EST was cloned from a human fetal kidney library using an in vivo cloning technique (Nsp1) in pRK5. There is a single long open reading frame

which encodes a 576 amino acid protein. The C-terminus of Nsp1 has no significant identity to any known mammalian proteins. This C-terminal sequence was then used to re-screen the EST database, wherein was found an additional fragment. From this sequence was constructed cloning and enrichment primers, and the corresponding full length sequence was isolated for Nsp3 using an in vivo cloning technique from a human placenta library in pRK5. The probes used for the cloning of the full length-sequences were the following:

- 5 Nsp1:
 Cloning: ACTGAGGCCTGTTGAAAGTGCAGAGCTCAG (SEQ ID NO:162)
 Enrichment Primer: GCTGAAGAAGAGCTTCAG (SEQ ID NO:163)
 Nsp3:
 Cloning: GGCCAGCATGATGGACATGGTGTGGAACCTTCCAGCAGGTCTAGGCGTA (SEQ ID
 10 NO:164)
 Enrichment Primer: GGTGCAGCCCAGGATGTC (SEQ ID NO:165)

- 15 Nsp3 has an SH2 domain and a potential SH3 interaction domain (PS region). The proteins lack apparent kinase or phosphatase domains. cDNA clones Nsp1 Nsp3 were sequenced in their entirety. The entire nucleotide sequence of DNA61601-1223 [Figure 13; SEQ ID NO:13] encoding PRO309 polypeptides [Figure 14; SEQ ID NO:14] has been deposited with ATCC March 31, 1998 and is assigned ATCC deposit number 209713.

EXAMPLE 10: Isolation of cDNA clones Encoding Human PRO332 Polypeptides [UNQ293]

- 20 Based upon an ECD homology search performed as described in Example 1 above, a consensus DNA sequence designated herein as DNA36688 was assembled. Based on the DNA36688 consensus sequence, oligonucleotides were synthesized to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for PRO332.

A pair of PCR primers (forward and reverse) were synthesized:

- 5'-GCATTGGCCGCGAGACTTTGCC-3' (SEQ ID NO:166)
 25 5'-GCGGCCACGGTCCTTGGAAATG-3' (SEQ ID NO:167)

A probe was also synthesized:

5'-TGGAGGAGCTCAACCTCAGCTACAACCGCATCACCAGCCCACAGG-3'
 (SEQ ID NO:168)

- 30 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO332 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from a human fetal liver library (LIB229).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for DNA40982-1235 and the derived protein sequence for PRO332.

- 35 The entire nucleotide sequence of DNA40982-1235 is shown in Figure 15 (SEQ ID NO:15). Clone DNA40982-1235 contains a single open reading frame (with an apparent translational initiation site at nucleotide positions 342-344, as indicated in Figure 15). The predicted polypeptide precursor is 642 amino acids long (Figure 16; SEQ ID NO:16), and has a calculated molecular weight of 72,067 (pI: 6.60). Clone DNA40982-1235 has been

deposited with ATCC November 7, 1997 and is assigned ATCC deposit no. ATCC 209433.

Based on a BLAST and FastA sequence alignment analysis of the full-length sequence, PRO332 shows about 30-40% amino acid sequence identity with a series of known proteoglycan sequences, including, for example, fibromodulin and fibromodulin precursor sequences of various species (FMOD BOVIN, FMOD CHICK, FMOD RAT, FMOD MOUSE, FMOD HUMAN, P R36773), osteomodulin sequences (AB000114 1, AB007848 1), decorin sequences (CFU83141 1, OCU03394 1, P R42266, P R42267, P R42260, P R89439), keratan sulfate proteoglycans (BTU48360 1, AF022890 1), corneal proteoglycan (AF022256 1), and bone/cartilage proteoglycans and proteoglycane precursors (PGS1 BOVIN, PGS2 MOUSE, PGS2 HUMAN).

EXAMPLE 11: Isolation of cDNA clones Encoding Human PRO356 (NL4) Polypeptides [UNO313]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST (#2939340) was identified which showed homology to human TIE-2 L1 and TIE-2 L2.

Based on the EST, a pair of PCR primers (forward and reverse), and a probe were synthesized:

NL4,5-1: 5'-TTCAGCACCAAGGACAAGGACAATGACAACT-3' (SEQ ID NO:169)

NL4,3-1: 5'-TGTGCACACTTGTCCAAGCAGTTGTCATTGTC-3' (SEQ ID NO:170)

NL4,3-3: 5'-GTAGTACACTCCATTGAGGTTGG-3' (SEQ ID NO:171).

Oligo dT primed cDNA libraries were prepared from uterus mRNA purchased from Clontech, Inc. (Palo Alto, CA, USA, catalog # 6537-1) in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized to greater than 1000 bp appropriately by gel electrophoresis, and cloned in a defined orientation into XhoI/NotI-cleaved pRK5D.

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO356 gene using the probe oligonucleotide and one of the PCR primers.

DNA sequencing of the clones isolated as described above gave a full-length DNA sequence DNA47470-1130P1 (SEQ ID NO:19; Figure 19) and the derived PRO356 protein (SEQ ID NO:20; Figure 20) shown in Figure 19 & 20 respectively.

The entire nucleotide sequence of DNA47470-1130P1 is shown in Figure 19 (SEQ ID NO:19). Clone DNA47470-1130P1 (SEQ ID NO:19) contains a single open reading frame with an apparent translation initiation site at nucleotide positions 215-217, and a TAA stop codon at nucleotide positions 1038-1040, as indicated by bolded underline. The predicted PRO356 polypeptide shown in Figure 20 is 346 amino acids long (SEQ ID NO:20), has a calculated molecular weight of 40,018 daltons and a pI of 8.19. A cDNA clone containing DNA47470-1130P1 (SEQ ID NO:19) has been deposited with ATCC on October 28, 1997 and is assigned ATCC deposit no. 209422.

Further analysis of the PRO356 polypeptide of Figure 20 (SEQ ID NO:20) reveals: a signal peptide at amino acid residues 1 to about 26, N-glycosylation sites at about residues 58-62, 253-257 and 267-271, glycosaminoglycan attachment sites at residues 167-171, a cAMP- and cGMP-dependent protein kinase

phosphorylation site at about residues 176-180, N-myristoylation sites at about residues 168-174, 196-202, 241-247, 252-258, 256-262, 327-333, a cell attachment sequence at about residues 199-202, and fibrinogen beta and gamma chains C-terminal domain proteins at about residues 160-198, 201-210, 219-256, 266-279, 283-313.

EXAMPLE 12: Isolation of cDNA clones Encoding Human PRO540 Polypeptides [UNQ341]

5 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA39631. Based on the DNA39631 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO540.

Forward and reverse PCR primers were synthesized:

10 forward PCR primer 5'-CTGGGGCTACACACGGGGTGAGG-3' (SEQ ID NO:172)

reverse PCR primer 5'-GGTGCCGCTGCAGAAAGTAGAGCG-3' (SEQ ID NO:173)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40654 sequence which had the following nucleotide sequence

hybridization probe

15 5'-GCCCCAAATGAAAACGGGCCCTACTTCCTGGCCCTCCGCGAGATG-3'
(SEQ ID NO:174)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO540 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO540 [herein designated as UNQ341 (DNA44189-1322)] (SEQ ID NO:21) and the derived protein sequence for PRO540.

The entire nucleotide sequence of UNQ341 (DNA44189-1322) is shown in Figure 21 (SEQ ID NO:21). Clone UNQ341 (DNA44189-1322) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 21-23 and ending at the stop codon at nucleotide positions 1257-1259 (Figure 21). The predicted polypeptide precursor is 412 amino acids long (Figure 22; SEQ ID NO:22). The full-length PRO540 protein shown in Figure 22 has an estimated molecular weight of about 46,658 daltons and a pI of about 6.65. Important regions of the amino acid sequence of PRO540 include the signal peptide, potential N-glycosylation sites, a potential lipid substrate binding site, a sequence typical of lipases and serine proteins, and a beta-transducin family Trp-Asp repeat. Clone UNQ341 (DNA44189-1322) has been deposited with ATCC on March 26, 1998 and is assigned ATCC deposit no. 209699.

EXAMPLE 13: Isolation of cDNA clones Encoding Human PRO618 Polypeptides [UNQ354]

35 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA30900. Based on the DNA30900 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO618.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-TAACAGCTGCCCCACTGCTTCCAGG-3' (SEQ ID NO:175)

reverse PCR primer 5'-TAATCCAGCAGTGCAGGCCGGG-3' (SEQ ID NO:176)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA30900

5 sequence which had the following nucleotide sequence

hybridization probe

5'-ATGGCCTCCACGGTGTGTGGACCGTGTTCCTGGGCAAGGTGTGGCAGAA-3'

(SEQ ID NO:177)

Screening of the above described library gave rise to the partial cDNA clone designated herein DNA3559.

10 Extension of this sequence using repeated cycles of BLAST and phrap gave rise to a nucleotide sequence designated herein as DNA43335. Primers based upon the DNA43335 consensus sequence were then prepared as follows.

forward PCR primer 5'-TGCCTATGCACTGAGGAGGCAGAAG-3' (SEQ ID NO:178)

reverse PCR primer 5'-AGGCAGGGACACAGAGTCCATTAC-3' (SEQ ID NO:179)

15 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA43335 sequence which had the following nucleotide sequence

hybridization probe

5'-AGTATGATTTGCCGTGCACCCAGGGCCAGTGGACGATCCAGAACAGGAGG-3'

(SEQ ID NO:180)

20 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate full length clones encoding the PRO618 gene using the second probe oligonucleotide and one of the second set of PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB229).

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO618 [herein designated as UNQ354 (DNA49152-1324)] (SEQ ID NO:23) and the derived protein sequence for PRO618.

The entire nucleotide sequence of UNQ354 (DNA49152-1324) is shown in Figure 23 (SEQ ID NO:23). Clone UNQ354 (DNA49152-1324) contains a single open reading frame with an apparent translational initiation
30 site at nucleotide positions 73-75 and ending at the stop codon at nucleotide positions 2479-2481 (Figure 23). The predicted polypeptide precursor is 802 amino acids long (Figure 24; SEQ ID NO:24). The full-length PRO618 protein shown in Figure 24 has an estimated molecular weight of about 88,846 daltons and a pI of about 6.41. Important regions of the amino acid sequence of PRO618 include type II transmembrane domain, a sequence typical of a protease, trypsin family, histidine active site, multiple N-glycosylation sites, two sequences typical of
35 a Kringle domain, two regions having sequence similarity to Kallikrein light chain, and a region having sequence similarity to low-density lipoprotein receptor. Clone UNQ354 (DNA49152-1324) has been deposited with ATCC on April 28, 1998 and is assigned ATCC deposit no. 209813.

EXAMPLE 14: Isolation of cDNA clones Encoding Human PRO944 Polypeptides [UNQ481]

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA47374. A variety of proprietary Genentech EST sequences were employed in the assembly. Based on the DNA47374 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO944.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CGAGCGAGTCATGGCCAACGC-3' (SEQ ID NO:181)

reverse PCR primer 5'-GTGTCACACGTAGTCTTTCCCGCTGG-3' (SEQ ID NO:182)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47374 sequence which had the following nucleotide sequence hybridization probe

5'-CTGCAGCTGTTGGGCTTCATTCTCGCCTTCTGGGATGGATCG-3' (SEQ ID NO:183)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO944 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO944 [herein designated as UNQ481 (DNA52185-1370)] (SEQ ID NO:25) and the derived protein sequence for PRO944.

The entire nucleotide sequence of UNQ481 (DNA52185-1370) is shown in Figure 25 (SEQ ID NO:25). Clone UNQ481 (DNA52185-1370) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 219-221 and ending at the stop codon at nucleotide positions 852-854 (Figure 25). The predicted polypeptide precursor is 211 amino acids long (Figure 26; SEQ ID NO:26). The full-length PRO944 protein shown in Figure 26 has an estimated molecular weight of about 22,744 daltons and a pI of about 8.51. Analysis of the full-length PRO944 sequence shown in Figure 26 (SEQ ID NO:26) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, transmembrane domains from about amino acid 82 to about amino acid 102, from about amino acid 118 to about amino acid 142 and from about amino acid 161 to about amino acid 187, a potential N-glycosylation site from about amino acid 72 to about amino acid 75, a sequence block having homology to PMP-22/EMP/MP20 family of proteins from about amino acid 70 to about amino acid 111 and a sequence block having homology to ABC-2 type transport system integral membrane protein from about amino acid 119 to about amino acid 133. Clone UNQ481 (DNA52185-1370) has been deposited with ATCC on May 14, 1998 and is assigned ATCC deposit no. 209861.

Analysis of the amino acid sequence of the full-length PRO944 polypeptide suggests that it possesses significant sequence similarity to the CPE-R protein, thereby indicating that PRO944 may be a novel CPE-R homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO944 amino acid sequence and the following Dayhoff sequences, AB000713_1, AB000714_1, AF035814_1, AF000959_1, HSU89916_1, EMP2_HUMAN, JC5732, CELF53B3_6, PM22_MOUSE and CGU49797_1.

EXAMPLE 15: Isolation of cDNA clones Encoding Human PRO994 Polypeptides [UNQ518]

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 157555. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing
5 homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55728.

10 In light of an observed sequence homology between the DNA55728 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2860366, the Incyte EST clone 2860366 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 27 and is herein designated as DNA58855-1422.

Clone DNA58855-1422 contains a single open reading frame with an apparent translational initiation site
15 at nucleotide positions 31-33 and ending at the stop codon at nucleotide positions 718-720 (Figure 27; SEQ ID NO:27). The predicted polypeptide precursor is 229 amino acids long (Figure 28; SEQ ID NO:28). The full-length PRO994 protein shown in Figure 28 has an estimated molecular weight of about 25,109 daltons and a pI of about 6.83. Analysis of the full-length PRO994 sequence shown in Figure 28 (SEQ ID NO:28) evidences the presence of the following: transmembrane domains from about amino acid 10 to about amino acid 31, from
20 about amino acid 50 to about amino acid 72, from about amino acid 87 to about amino acid 110 and from about amino acid 191 to about amino acid 213, potential N-glycosylation sites from about amino acid 80 to about amino acid 83, from about amino acid 132 to about amino acid 135, from about amino acid 148 to about amino acid 151 and from about amino acid 163 to about amino acid 166 and an amino acid block having homology to TNFR/NGFR cysteine-rich region proteins from about amino acid 4 to about amino acid 11. Clone
25 DNA58855-1422 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203018.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 28 (SEQ ID NO:28), evidenced significant homology between the PRO994 amino acid sequence and the following Dayhoff sequences: AF027204_1, TAL6_HUMAN, ILT4_HUMAN, JC6205, MMU57570_1, S40363, ETU56093_1, S42858, P_R66849 and
30 P_R74751.

EXAMPLE 16: Isolation of cDNA clones Encoding Human PRO1079 Polypeptides [UNQ536]

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above, and is herein designated DNA52714. Based on information provided by the assembly, the clone
35 for Merck EST no. HO6898 was obtained and sequenced, thereby giving the nucleotide sequence designated herein as DNA56050-1455. The entire nucleotide sequence of DNA56050-1455 is shown in Figure 29 (SEQ ID NO:29). Clone DNA56050-1455 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 183-185 and ending at the stop codon at nucleotide positions 861-863 (Figure 29). The

predicted polypeptide precursor is 226 amino acids long (Figure 30; SEQ ID NO:30). The full-length PRO1079 protein shown in Figure 30 has an estimated molecular weight of about 24,611 Daltons and a pI of about 4.85. Analysis of the full-length PRO1079 sequence shown in Figure 30 (SEQ ID NO:30) evidences the presence of the following features: a signal peptide at about amino acid 1-29; potential N-myristoylation sites at about amino acids 10-15, and 51-56; homology to photosystem I psaG and psaK proteins at about amino acids 2 to 20; and homology to prolyl endopeptidase family serine proteins at about amino acids 150 to 163.

Analysis of the amino acid sequence of the full-length PRO1079 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO1079 amino acid sequence and the following Dayhoff sequences: CEK10C3_4, MMU50734_1, D69503, AF051149_1, and VSMP_CVMS.

Clone UNQ536 (DNA56050-1455) was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no. 203011.

EXAMPLE 17: Isolation of cDNA clones Encoding Human PRO1110 Polypeptides [UNQ553]

A cDNA clone (DNA58727-1474) encoding a native human PRO1110 polypeptide was identified by a yeast screen, in a human fetal kidney cDNA library that preferentially represents the 5' ends of the primary cDNA clones. The yeast screen employed identified a single EST clone designated herein as DNA45566. The DNA45566 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA46965. Oligonucleotide primers based upon the DNA46965 sequence were then synthesized and employed to screen a human SK-Lu-1 adenocarcinoma cDNA library (LIB247) which resulted in the identification of the DNA58727-1474 clone shown in Figure 31.

The full-length DNA58727-1474 clone shown in Figure 31 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 131-133 and ending at the stop codon at nucleotide positions 1097-1099 (Figure 31; SEQ ID NO:31). The predicted polypeptide precursor is 322 amino acids long (Figure 32; SEQ ID NO:32). The full-length PRO1110 protein shown in Figure 32 has an estimated molecular weight of about 35,274 daltons and a pI of about 8.57. Analysis of the full-length PRO1110 sequence shown in Figure 32 (SEQ ID NO:32) evidences the presence of the following: transmembrane domains from about amino acid 41 to about amino acid 60, from about amino acid 66 to about amino acid 85, from about amino acid 101 to about amino acid 120, from about amino acid 137 to about amino acid 153, from about amino acid 171 to about amino acid 192, from about amino acid 205 to about amino acid 226, from about amino acid 235 to about amino acid 255 and from about amino acid 294 to about amino acid 312, a potential N-glycosylation site from about amino acid 6 to about amino acid 69, and a glycosaminoglycan attachment site from about amino acid 18 to about amino acid 21. Clone DNA58727-1474 has been deposited with ATCC on September 1, 1998 and is assigned ATCC deposit no. 203171.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence

alignment analysis of the full-length sequence shown in Figure 32 (SEQ ID NO:32), evidenced significant homology between the PRO1110 amino acid sequence and the following Dayhoff sequences: MMMYELUPR_1, P_R99799, MAL_HUMAN, P_P80929, RNMALGENE_1, S68406, PLLP_RAT, MMMALPROT_1, I38891 and S55622.

5 EXAMPLE 18: Isolation of cDNA clones Encoding Human PRO1122 Polypeptides [UNQ561]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified. The EST was Incyte 1347523 also called DNA49665. Based on DNA49665, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolated a clone of the full-length coding sequence for the PRO1122. [e.g.,
10 Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989); Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probes sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5
15 kpb. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward, reverse and hybridization) were synthesized:
20 forward PCR primer: 5'-ATCCACAGAAGCTGGCCTTCGCCG-3' (SEQ ID NO:184)
reverse PCR primer: 5'-GGGACGTGGATGAACTCGGTGTGG-3' (SEQ ID NO:185)
hybridization probe:
5'-TATCCACAGAAGCTGGCCTTCGCCGAGTGCCTGTGCAGAG-3' (SEQ ID NO:186).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened
25 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1122 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue. The cDNA libraries used to isolate the cDNA clones were constructed using standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI
30 site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 235: 1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for
35 PRO1122 [herein designated as DNA62377-1381-1](SEQ ID NO:33) and the derived protein PRO1122 sequence (UNQ561)(SEQ ID NO:34).

The entire nucleotide sequence of DNA62377-1381-1 (SEQ ID NO:33) is shown in Figure 33 (SEQ ID NO:33). Clone DNA62377-1381-1 (SEQ ID NO:33) contains a single open reading frame with an apparent

translational initiation site at nucleotide positions 50-52 and ending at the stop codon at nucleotide positions 641-643 of SEQ ID NO:33 (Figure 33). The predicted polypeptide precursor is 197 amino acids long (Figure 34; SEQ ID NO:34). The full-length PRO1122 protein shown in Figure 34 (UNQ561)(SEQ ID NO:34) has an estimated molecular weight of about 21765 daltons and a pI of about 8.53. Clone DNA62377-1381-1 has been deposited with the ATCC on December 22, 1998 and has been assigned deposit number 203552. It is understood that in the event of a sequencing irregularity or error in the sequences provided herein, the correct sequence is the sequence deposited. Furthermore, all sequences provided herein are the result of known sequencing techniques.

Analysis of the amino acid sequence of the isolated full-length PRO1122 (UNQ561) suggests that it possesses similarity with IL-17, thereby indicating that PRO1122 (UNQ561) may be a novel cytokine and is herein designated IL-17C. Figure 34 (SEQ ID NO:34) also shows the approximate locations of the signal peptide, leucine zipper pattern, and a region having sequence identity with IL-17.

EXAMPLE 19: Isolation of cDNA clones Encoding Human PRO1138 Polypeptides [UNQ576]

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence, Incyte cluster sequence no. 165212. This cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated as DNA54224. The assembly included a proprietary Genentech EST designated herein as DNA49140.

In light of an observed sequence homology between the DNA54224 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3836613, the Incyte EST clone 3836613 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 35 and is the full-length DNA sequence for PRO1138. Clone DNA58850-1495 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209956.

The entire nucleotide sequence of DNA58850-1495 is shown in Figure 35 (SEQ ID NO:35). Clone DNA58850-1495 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 38-40 and ending at the stop codon at nucleotide positions 1043-1045 (Figure 35). The predicted polypeptide precursor is 335 amino acids long (Figure 36; SEQ ID NO:36). The full-length PRO1138 protein shown in Figure 36 has an estimated molecular weight of about 37,421 Daltons and a pI of about 6.36. Analysis of the full-length PRO1138 sequence shown in Figure 36 (SEQ ID NO:36) evidences the presence of the following features: a signal peptide at about amino acid 1 to about amino acid 22; a transmembrane domain at about amino acids 224 to about 250; a leucine zipper pattern at about amino acids 229 to about 250; and potential N-glycosylation sites at about amino acids 98-101, 142-145, 148-151, 172-175, 176-179, 204-207, and 291-295.

Analysis of the amino acid sequence of the full-length PRO1138 polypeptide suggests that it possesses significant sequence similarity to the CD84, thereby indicating that PRO1138 may be a novel member of the Ig

superfamily of polypeptides. More particularly, analysis of the amino acid sequence of the full-length PRO1138 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1138 amino acid sequence and the following Dayhoff sequences: HSU82988_1, HUMLY9_1, P_R97631, P_R97628, P_R97629, P_R97630, CD48_RAT, CD2_HUMAN, P_P93996, and HUMBGP_1.

5 Clone DNA58850-1495 was deposited with ATCC on June 9, 1998, and is assigned ATCC deposit no. 209956.

EXAMPLE 20: Isolation of cDNA clones Encoding Human PRO1190 Polypeptides [UNQ604]

10 The method described in Example 1 above allowed the identification of a single Merck/Washington University EST sequence, EST no. AA339802, which is designated herein as "DNA53943". Based on the DNA53943 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1190.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: (53943.f1) GGGAAACACAGCAGTCATTGCCTGC (SEQ ID NO:187)

reverse PCR primer: (53943.r1) GCACACGTAGCCTGTCGCTGGAGC (SEQ ID NO:188)

15 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA53943 sequence which had the following nucleotide sequence:

hybridization probe: (53943.p1) CACCCCAAAGCCCAGGTCCGGTACAGCGTCAAACAAGAGTGG (SEQ ID NO:189)

20 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1190 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow.

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1190 (designated herein as DNA59586-1520 [Figure 37, SEQ ID NO:37]; and the derived protein sequence for PRO1190.

30 The entire coding sequence of PRO1190 is shown in Figure 37 (SEQ ID NO:37). Clone DNA59586-1520 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 340-342 and an apparent stop codon at nucleotide positions 3685-3687. The predicted polypeptide precursor is 1115 amino acids long. The full-length PRO1190 protein shown in Figure 38 (SEQ ID NO:38) has an estimated molecular weight of about 121,188 daltons and a pI of about 7.07. Other features of the PRO1190 protein include: two transmembrane domains at amino acids 16-30 and 854-879; a cytochrome P450 cysteine heme-iron ligand signature at amino acids 1051-1060; an N-6 adenine-specific DNA methylases signature at amino acids 1045-1051; and potential N-glycosylation sites at amino acids 65-68, 76-79, 98-101, 189-192, 275-278, 518-521, 726-729, and 760-763. Clone DNA59586-1520 was deposited with the ATCC on September 29, 1998, and is assigned
35 ATCC deposit no. 203288.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 38 (SEQ ID NO:38), revealed homology between the PRO1190 amino acid sequence and the following Dayhoff sequences: AF004840_1, AF004841_1,

AF026465_1, HSU72391_1, P_R13144, AXO1_HUMAN, GEN13349, I58164, D87212_1, A53449, and D86983_1, and KIAA0230.

EXAMPLE 21: Isolation of cDNA clones Encoding Human PRO1272 Polypeptides [UNQ642]

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that
10 did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA58753.

In light of an observed sequence homology between the DNA58753 sequence and an EST sequence contained within the EST clone 3049165, the Incyte clone (from a lung library) including EST 3049165 was
15 purchased and the cDNA insert was obtained and sequenced. The sequence of this cDNA insert is shown in Figure 39 and is herein designated as DNA64896-1539.

The full length clone shown in Figure 39 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon found at nucleotide positions 556-558 (Figure 39; SEQ ID NO:39). The predicted polypeptide precursor (Figure 40, SEQ ID NO:40) is 166
20 amino acids long. The signal peptide is at about amino acids 1-23 of SEQ ID NO:40. PRO1272 has a calculated molecular weight of approximately 19,171 daltons and an estimated pI of approximately 8.26. Clone DNA64896-1539 was deposited with the ATCC on September 9, 1998 and is assigned ATCC deposit no. 203238.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 40 (SEQ ID NO:40), revealed sequence identity
25 between the PRO1272 amino acid sequence and the following Dayhoff sequences (information from database incorporated herein): AF025474_1, D69100, AE000757_10, H69466, CELC50E3_12, XLRANBP1_1, YD67_SCHPO, B69459, H36856, and FRU40755_1.

EXAMPLE 22: Isolation of cDNA clones Encoding Human PRO1286 Polypeptides [UNQ655]

30 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, designated EST Cluster No. 86809. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or
35 BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). ESTs in the assembly included those identified from tumors, cell lines, or diseased tissue. One or

more of the ESTs was obtained from a cDNA library constructed from RNA isolated from diseased colon tissue. The consensus sequence obtained therefrom is herein designated DNA58822.

In light of the sequence homology between the DNA58822 sequence and an EST sequence contained within EST no. 1695434, EST clone no. 1695434 was purchased and the cDNA insert was obtained and sequenced. The sequence of this cDNA insert is shown in Figure 41 and is herein designated DNA64903-1553 (SEQ ID NO:41).

The full length clone shown in Figure 41 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 93-95 and ending at the stop codon found at nucleotide positions 372-374 (Figure 41; SEQ ID NO:41). The predicted polypeptide precursor (Figure 42, SEQ ID NO:42) is 93 amino acids long, with a signal sequence at about amino acids 1-18. PRO1286 has a calculated molecular weight of approximately 10,111 daltons and an estimated pI of approximately 9.70.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 42 (SEQ ID NO:42), revealed some homology between the PRO1286 amino acid sequence and the following Dayhoff sequences: SR5C_ARATH, CELC17H12_11, MCPD_ENTAE, JQ2283, INVO_LEMCA, P_R07309, ADEVBCAGN_4, AF020947_1, CELT23H2_1, and MDH_STRAR.

Clone DNA64903-1553 was deposited with the ATCC on September 15, 1998 and is assigned ATCC deposit no. 203223.

EXAMPLE 23: Isolation of cDNA clones Encoding Human PRO1295 Polypeptides [UNQ664]

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. One or more of the ESTs was derived from a thymus tissue library. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56262.

In light of the sequence homology between the DNA56262 sequence and an EST contained within the Incyte EST 3743334, the clone including this EST was purchased and the cDNA insert was obtained and sequenced. The sequence of this cDNA insert is shown in Figure 43 and is herein designated as DNA59218-1559.

The full length clone shown in Figure 43 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 207-209 and ending at the stop codon found at nucleotide positions 1047-1049 (Figure 43; SEQ ID NO:43). The predicted polypeptide precursor (Figure 44, SEQ ID NO:44) is 280 amino acids long. The signal peptide is at about amino acids 1-18 of SEQ ID NO:44. A targeting signal and N-glycosylation site are also indicated in Figure 44. PRO1295 has a calculated molecular weight of approximately 30,163 daltons and an estimated pI of approximately 6.87. Clone DNA59218-1559 was deposited with the ATCC on September 29, 1998 and is assigned ATCC deposit no. 203287.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 44 (SEQ ID NO:44), revealed sequence identity between the PRO1295 amino acid sequence and the following Dayhoff sequences (data incorporated herein): AB011099_1, ILVE_MYCTU, ATTECR_2, AF010496_27, P_R15346, S37191, PER_DROMS, L2MU_ADECC and P_W34238.

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EXAMPLE 24: Isolation of cDNA clones Encoding Human PRO1309 Polypeptides [UNQ675]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to SLIT.

RNA for construction of cDNA libraries was isolated from human fetal brain tissue. The cDNA libraries used to isolate the cDNA clones encoding human PRO1309 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

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The cDNA libraries (prepared as described above), were screened by hybridization with a synthetic oligonucleotide probe derived from the above described Incyte EST sequence:

5'-TCCGTGCAGGGGACGCCTTTCAGAACTGCGCCGAGTTAAGGAAC-3' (SEQ ID NO:190).

A cDNA clone was isolated and sequenced in entirety. The entire nucleotide sequence of DNA59588-1571 is shown in Figure 45 (SEQ ID NO:45). Clone DNA59588-1571 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 720-722 and a stop codon at nucleotide positions 2286-2288 (Figure 45; SEQ ID NO:45). The predicted polypeptide precursor is 522 amino acids long (Figure 46; SEQ ID NO:46). The signal peptide is approximately at 1-34 and the transmembrane domain is at approximately 428-450 of SEQ ID NO:278. Clone DNA59588-1571 has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203106. The full-length PRO1309 protein shown in Figure 46 has an estimated molecular weight of about 58,614 daltons and a pI of about 7.42.

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An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 46 (SEQ ID NO:46), revealed sequence identity between the PRO1309 amino acid sequence and the following Dayhoff sequences: AB007876_1, GPV_MOUSE, ALS_RAT, P_R85889, LUM_CHICK, AB014462_1, PGS1_CANFA, CEM88_7, A58532 and GEN11209.

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EXAMPLE 25: Isolation of cDNA clones Encoding Human PRO1316 Polypeptides [UNQ682]

The extracellular domain (ECD) which includes the signal sequence, if any, of publicly available databases known to contain secreted sequences were used to search various publicly available EST (Expressed Sequenced Tag) databases (GenBank, Merck/Wash. U). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology 266: 460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled

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into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

The above search resulted in the identification of the EST, designated W55979 which showed homology with the secreted protein Dkk-1. The clone corresponding to EST W55979 (clone NbHH19W) was purchased from Merck/Washington University and the cDNA insert was obtained and sequenced in its entirety.

The nucleic acid sequence corresponding to the full length PRO1316 (designated DNA60608-1577) encoded by the purchased clone, is shown in Figure 47 (SEQ ID NO:47). DNA60608-1577 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 211-213, and a stop codon at nucleotide positions 988-990 (Figure 47; SEQ ID NO:47). The predicted polypeptide precursor is 259 amino acids long (Figure 48; SEQ ID NO:48). Additional regions of significant interest include the nucleotide residues encoding the signal peptide (211-283), an N-glycosylation site (364-366), and the Zn(2)-Cys(6) binuclear cluster domain (505-655). Clone DNA60608-1577 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203126. The full-length PRO1316 protein shown in Figure 48 has an estimated molecular weight of about 28,447 daltons and a pI of about 9.48.

Based on a BLAST and FastA sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1316 shows significant amino acid sequence identity to the dickkopf family of proteins. Additionally, DNA60608 has shown homology to AF030433_1, LFE4_CHICK, COL_RABIT, YQI6_CAEEL, ITB6_HUMAN, CONO_LYMST, S41033, D63483_1, D86864_1 and AB001978_1.

EXAMPLE 26: Isolation of cDNA clones Encoding Human PRO1383 Polypeptides [UNQ7191]

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA53961. Based on the DNA53961 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1383.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CATTTCCCTTACCCTGGACCCAGCTCC-3' (SEQ ID NO:191)

reverse PCR primer 5'-GAAAGGCCACAGCACATCTGGCAG-3' (SEQ ID NO:192)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA53961 sequence which had the following nucleotide sequence

hybridization probe

5'-CCACGACCCGAGCAACTTCCTCAAGACCGACTTGTTTCTCTACAGC-3' (SEQ ID NO:193)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1383 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1383 (designated herein as DNA58743-1609 [Figure 49, SEQ ID NO: 49]) and the derived protein sequence for PRO1383.

The entire nucleotide sequence of DNA58743-1609 is shown in Figure 49 (SEQ ID NO:49). Clone DNA58743-1609 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 122-124 and ending at the stop codon at nucleotide positions 1391-1393 (Figure 49). The predicted polypeptide precursor is 423 amino acids long (Figure 50; SEQ ID NO:50). The full-length PRO1383 protein shown in Figure 50 has an estimated molecular weight of about 46,989 daltons and a pI of about 6.77. Analysis of the full-length PRO1383 sequence shown in Figure 50 (SEQ ID NO:50) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a transmembrane domain from about amino acid 339 to about amino acid 362, and potential N-glycosylation sites from about amino acid 34 to about amino acid 37, from about amino acid 58 to about amino acid 61, from about amino acid 142 to about amino acid 145, from about amino acid 197 to about amino acid 200, from about amino acid 300 to about amino acid 303 and from about amino acid 364 to about amino acid 367. Clone DNA58743-1609 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203154.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 50 (SEQ ID NO:50), evidenced significant homology between the PRO1383 amino acid sequence and the following Dayhoff sequences: NMB_HUMAN, QNR_COTJA, P_W38335, P115_CHICK, P_W38164, A45993_1, MMU70209_1, D83704_1 and P_W39176.

EXAMPLE 27: Isolation of cDNA clones Encoding Human PRO1384 Polypeptides [UNQ721]

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA54192. Based on the DNA54192 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1384.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGCAGCCCCTGTGACACAAACTGG-3' (SEQ ID NO:194)

reverse PCR primer 5'-CTGAGATAACCGAGCCATCCTCCAC-3' (SEQ ID NO:195)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA54192 sequence which had the following nucleotide sequence:

hybridization probe

5'-GGAGATAGCTGCTATGGGTTCTTCAGGCACAACCTTAACATGGGAAG-3' (SEQ ID NO:196)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1384 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1384 (designated herein as DNA71159-1617 [Figure 51, SEQ ID NO:51]; and the derived protein sequence for PRO1384.

The entire coding sequence of PRO1384 is shown in Figure 51 (SEQ ID NO:51). Clone DNA71159-1617 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 182-184 and an apparent stop codon at nucleotide positions 869-871. The predicted polypeptide precursor is 229 amino acids long (Figure 52; SEQ ID NO:52). The full-length PRO1384 protein shown in Figure 52 has an estimated molecular weight of about 26,650 daltons and a pI of about 8.76. Additional features include a type II

transmembrane domain at about amino acids 32-57, and potential N-glycosylation sites at about amino acids 68-71, 120-123, and 134-137.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 52 (SEQ ID NO:52), revealed homology between the PRO1384 amino acid sequence and the following Dayhoff sequences: AF054819_1, HSAJ1687_1, AF009511_1, AB010710_1, GEN13595, HSAJ673_1, GEN13961, AB005900_1, LECH_CHICK, AF021349_1, and NK13_RAT.

Clone DNA71159-1617 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203135.

10 EXAMPLE 28: Isolation of cDNA clones Encoding Human PRO1431 Polypeptides [UNQ737]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST (isolated from adult brain stem tissue) was identified (1370141, DNA66505) which showed homology to SH3. RNA for construction of cDNA libraries was isolated from human bone marrow. A full length cDNA corresponding to the isolated EST was isolated using an in vitro cloning technique (DNA73401-1633) in pRK5.

The cDNA libraries used to isolate the cDNA clones encoding human PRO1431 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

A cDNA clone was sequenced in entirety. The entire nucleotide sequence of DNA73401-1633 (SEQ ID NO:53) is shown in Figure 53. Clone DNA73401-1633 contains a single open reading frame with an apparent translational initiation site at about nucleotide positions 630-632 and a stop codon at about nucleotide positions 1740-1742. The predicted polypeptide precursor encoded by DNA73401-1633 is 370 amino acids long (Figure 54; SEQ ID NO:54). Clone DNA73401 (designated as DNA73402-1633) has been deposited with ATCC on September 22, 1998 and is assigned ATCC deposit no. 203273.

Based sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1431 shows significant amino acid sequence identity to SH17_HUMAN, an SH3 containing protein known as SH3P17. Additional significant identity score were found with D89164_1, AF032118_1, EXLP_TOBAC, YHR4_YEAST, S46992, RATP130CAS_2, AF043259_1, RATP130CAS_1 and MYSC_ACACA.

30 EXAMPLE 29: Isolation of cDNA clones Encoding Human PRO1434 Polypeptides [UNQ739]

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA54187. Based on the DNA54187 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1434.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GAGGTGTCGCTGTGAAGCCAACGG-3' (SEQ ID NO:197)

reverse PCR primer 5'-CGCTCGATTCTCCATGTGCCTTCC-3' (SEQ ID NO:198)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA54187 sequence which had the following nucleotide sequence

hybridization probe

5 5'-GACGGAGTGTGTGGACCCTGTGTACGAGCCTGATCAGTGCTGTCC-3' (SEQ ID NO:199)

RNA for construction of the cDNA libraries was isolated from human retina tissue (LIB94).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1434 (designated herein as DNA68818-2536 [Figure 55, SEQ ID NO:55]; and the derived protein sequence for PRO1434.

10 The entire nucleotide sequence of DNA68818-2536 is shown in Figure 55 (SEQ ID NO:55). Clone DNA68818-2536 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 581-583 and ending at the stop codon at nucleotide positions 1556-1558 (Figure 55). The predicted polypeptide precursor is 325 amino acids long (Figure 56; SEQ ID NO:56). The full-length PRO1434 protein shown in Figure 56 has an estimated molecular weight of about 35,296 daltons and a pI of about 5.37. Analysis
15 of the full-length PRO1434 sequence shown in Figure 56 (SEQ ID NO:56) evidences the presence of a variety of important protein domains as shown in Figure 56. Clone DNA68818-2536 has been deposited with ATCC on February 9, 1999 and is assigned ATCC deposit no. 203657.

20 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 56 (SEQ ID NO:56), evidenced significant homology between the PRO1434 amino acid sequence and the following Dayhoff sequences: NEL_MOUSE, APMU_PIG, P_W37501, NEL_RAT, TSP1_CHICK, P_W37500, NEL2_HUMAN, MMU010792_1, D86983_1 and 10 MUCS_BOVIN.

EXAMPLE 30: Isolation of cDNA clones Encoding Human PRO1475 Polypeptides [UNQ746]

25 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA45639. Based on the DNA45639 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1475.

PCR primers (forward and reverse) were synthesized:

30 forward PCR primer (45639.f1) 5'-GATGGCAAAACGTGTGTTTGACACG-3' (SEQ ID NO:200)

forward PCR primer (45639.f2) 5'-CCTCAACCAGGCCACGGGCCAC-3' (SEQ ID NO:201)

reverse PCR primer (45639.r1) 5'-CCCAGGCAGAGATGCAGTACAGGC-3' (SEQ ID NO:202)

reverse PCR primer (45639.r2) 5'-CCTCCAGTAGGTGGATGGATTGGCTC-3' (SEQ ID NO:203)

35 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45639 sequence which had the following nucleotide sequence

hybridization probe (45639.p1)

5'-CTCACCTCATGAGGATGAGGCCATGGTGCTATTCCTCAACATGGTAG-3' (SEQ ID NO:204)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened

by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1475 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1475 (designated herein as DNA61185-1646 [Figure 57, SEQ ID NO:57]; and the derived protein sequence for PRO1475.

The entire nucleotide sequence of DNA61185-1646 is shown in Figure 57 (SEQ ID NO:57). Clone DNA61185-1646 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 130-132 and ending at the stop codon at nucleotide positions 2110-2112 (Figure 57). The predicted polypeptide precursor is 660 amino acids long (Figure 58; SEQ ID NO:58). The full-length PRO1475 protein shown in Figure 58 has an estimated molecular weight of about 75,220 daltons and a pI of about 6.76. Analysis of the full-length PRO1475 sequence shown in Figure 58 (SEQ ID NO:58) evidences the presence of the following: a transmembrane domain from about amino acid 38 to about amino acid 55 and a homologous region to mouse GNT1 from about amino acid 229 to about amino acid 660. Clone DNA61185-1646 has been deposited with ATCC on November 17, 1998 and is assigned ATCC deposit no. 203464.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 58 (SEQ ID NO:58), evidenced significant homology between the PRO1475 amino acid sequence and the following Dayhoff sequences: GNT1_MOUSE, CGU65792_1, CGU65791_1, P_R24781, CELF48E3_1, G786_HUMAN, P_W06547, GNT1_CAEL, 219_HUMAN and EF07_MOUSE.

EXAMPLE 31: Isolation of cDNA clones Encoding Human PRO1481 Polypeptides [UNQ750]

An initial DNA sequence, referred to herein as DNA53254, was identified using a yeast screen, in a human fetal kidney cDNA library that preferentially represents the 5' ends of the primary cDNA clones. Based on the DNA53254 sequence, oligonucleotides were synthesized for use as probes (or primers) to isolate a clone of the full-length coding sequence for PRO1481 from a human fetal kidney cDNA library.

The full length DNA58732-1650 clone shown in Figure 59 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 320-322 and ending at the stop codon found at nucleotide positions 1322-1324 (Figure 59; SEQ ID NO:59). The predicted polypeptide precursor (Figure 60, SEQ ID NO:60) is 334 amino acids long. The signal peptide is at about amino acids 1-23, and a transmembrane domain is at about amino acids 235-262 of SEQ ID NO:60. The N-glycosylation sites are indicated in Figure 60. PRO1481 has a calculated molecular weight of approximately 36,294 daltons and an estimated pI of approximately 4.98. Clone DNA58732-1650 has been deposited with the ATCC on September 29, 1998 and is assigned ATCC deposit no. 203290.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 60 (SEQ ID NO:60), revealed sequence identity between the PRO1481 amino acid sequence and the following Dayhoff sequences (data incorporated herein): YN23_YEAST, S67770, H36857, YLU2_PICAN, GEN12881, CVY15035_28, YM96_YEAST, ESC1_SCHPO, CELZK783_1 and S59310.

EXAMPLE 32: Isolation of cDNA clones Encoding Human PRO1568 Polypeptides [UNQ774]

A consensus DNA sequence was assembled relative to other EST sequences using phrap to form an assembly as described in Example 1 above. The consensus sequence is designated herein "DNA54208". Based on the DNA54208 consensus sequence, the assembly and other information and discoveries provided herein, a clone including an EST in the assembly was ordered and sequenced. The EST is Incyte.3089490. Sequencing in full gave the sequence shown in Figure 61.

The entire coding sequence of PRO1568 is included in Figure 61 (SEQ ID NO:61). Clone DNA68880-1676 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 208-210 and an apparent stop codon at nucleotide positions 1123-1125 of SEQ ID NO:61. The predicted polypeptide precursor is 305 amino acids long (Figure 62; SEQ ID NO:62). The signal peptide, transmembrane regions, N-myristoylation and amidation sites are also indicated in Figure 62. Clone DNA68880-1676 has been deposited with the ATCC on October 6, 1998 and is assigned ATCC deposit no. 203319. The full-length PRO1568 protein shown in Figure 62 has an estimated molecular weight of about 35,383 daltons and a pI of about 5.99.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 62 (SEQ ID NO:62), revealed sequence identity between the PRO1568 amino acid sequence and the following Dayhoff sequences (incorporated herein): AF089749_1, AF054841_1, NAG2_HUMAN, CD63_HUMAN, CD82_HUMAN, P_W05732, P_R86834, A15_HUMAN, P_W27333 and CD37_HUMAN.

EXAMPLE 33: Isolation of cDNA clones Encoding Human PRO1573 Polypeptides [UNQ779]

EST 3628990 was identified in an Incyte Database, (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) and extended in a comparison to other sequences in databases to form an assembly. The alignment search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence is designated herein "DNA69561".

Based on the DNA69561 consensus sequence and other information provided herein, a clone including another EST (Incyte DNA3752657) from the assembly was purchased and sequenced. This clone came from a breast tumor tissue library.

The entire coding sequence of PRO1573 is included in Figure 63 (SEQ ID NO:63). Clone DNA73735-1681 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 97-99 and an apparent stop codon at nucleotide positions 772-774. The predicted polypeptide precursor is 225 amino acids long (Figure 64; SEQ ID NO:64). The signal peptide is at about amino acids 1-17 and the transmembrane domains are at about amino acids 82-101, 118-145, and 164-188 of SEQ ID NO:64. One or more of the transmembrane domains can be deleted or inactivated. A phosphorylation site, amidation site, and N-myristoylation sites are shown in Figure 64. Clone DNA73735-1681 has been deposited with ATCC on October 20, 1998 and is assigned ATCC deposit no. 203356. The full-length PRO1573 protein shown in Figure 64 has

an estimated molecular weight of about 24,845 daltons and a pI of about 9.07.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 64 (SEQ ID NO:64), revealed sequence identity between the PRO1573 amino acid sequence and the following Dayhoff sequences (incorporated herein): AF007189_1, AB000714_1, AB000713_1, AB000712_1, A39484, AF000959_1, AF072127_, AF072128_1, AF068863_1 and AF077739_1.

EXAMPLE 34: Isolation of cDNA clones Encoding Human PRO1599 Polypeptides [UNQ782]

Incite EST no. 1491360 was identified as a sequence of interest using the techniques described in Example 1 above having a BLAST score of 70 or greater that does not encode a known protein. The nucleotide sequence of EST no. 1491360 and its complementary sequence is designated herein "DNA37192". Based on the DNA37192 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1599.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: GACGTCTGCAACAGCTCCTGGAAG (37192.f1; SEQ ID NO:205)

reverse PCR primer: CGAGAAGGAAACGAGGCCGTGAG (37192.r1; SEQ ID NO:206)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA37192 sequence which had the following nucleotide sequence:

hybridization probe: TGACACTTACCATGCTCTGCACCCGAGTGGGGACAGCCACAGA (SEQ ID NO:207).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1599 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1599 (designated herein as DNA62845-1684 [Figure 65, SEQ ID NO:65]; and the derived protein sequence for PRO1599.

The entire coding sequence of PRO1599 is shown in Figure 65 (SEQ ID NO:65). Clone DNA62845-1684 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 69-71 and an apparent stop codon at nucleotide positions 918-920. The predicted polypeptide precursor is 283 amino acids long (Figure 66; SEQ ID NO:66). The full-length PRO1599 protein shown in Figure 66 has an estimated molecular weight of about 30,350 daltons and a pI of about 9.66. Additional features of PRO1599 include: a signal peptide at about amino acids 1-30; potential N-glycosylation sites at about amino acids 129-132 and 189-192; a potential cAMP and cGMP-dependent protein kinase phosphorylation site at about amino acids 263-266; potential N-myristoylation sites at about amino acids 28-33, 55-60, 174-179, and 236-241; a potential amidation site at about amino acids 144-147; and a serine protease, trypsin family, histidine active site at about amino acids 70-75.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 66 (SEQ ID NO:66), revealed significant homology between the PRO1599 amino acid sequence and the following Dayhoff sequence: CFAD_PIG. Homology was

also found between the PRO1599 amino acids sequence and the following additional Dayhoff sequences. CFAD_HUMAN; P_R05421; P_R55757; P_R05772; GRAM_HUMAN; MUSLMET_1; P_P80335; P_R55758; A42048_1; and P_W05383.

Clone DNA62845-1684 was deposited with the ATCC on October 20, 1998 and is assigned ATCC deposit no. 203361.

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EXAMPLE 35: Isolation of cDNA clones Encoding Human PRO1604 Polypeptides [UNQ785]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched. Incyte EST No. 3550440 was identified as having homology to HDGF. EST No. 3550440 was then compared to various EST databases including public EST databases (e.g. GenBank), and the LIFESEQ® database, to identify homologous EST sequences. The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is designated herein "DNA67237".

In light of the sequence homology between the DNA67237 sequence and EST no. 3367060 from the LIFESEQ® database, the clone containing Incyte EST No. 3367060 was purchased and the cDNA insert was obtained and sequenced to obtain the entire coding sequence of PRO1604 which is shown in Figure 67 (SEQ ID NO:67).

Clone DNA71286-1687 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 65-67 and an apparent stop codon at nucleotide positions 2078-2080. The predicted polypeptide precursor is 671 amino acids long (Figure 68; SEQ ID NO:68). The full-length PRO1604 protein shown in Figure 68 has an estimated molecular weight of about 74,317 daltons and a pI of about 7.62. Additional features include a signal peptide at about amino acids 1-13; potential cAMP- and cGMP-dependent protein kinase phosphorylation sites at about amino acids 156-159, 171-174, and 451-454; potential N-myristoylation sites at about amino acids 46-51, 365-370, and 367-372; and a cell attachment sequence at about amino acids 661-663.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 68 (SEQ ID NO:68), revealed significant homology between the PRO1604 amino acid sequence and Dayhoff sequence no. P_W37483. Homology was also shown between the PRO1604 amino acid sequence and the following additional Dayhoff sequences: AF063020_1, P_R66727, P_W37482, JC5661, CEC25A1_11, CEU33058_1, I38073, MST2_DROHY, and HSATRX36_1.

Clone DNA71286-1687 was deposited with the ATCC on October 20, 1998, and is assigned ATCC deposit no. 203357.

EXAMPLE 36: Isolation of cDNA clones Encoding Human PRO1605 Polypeptides [UNQ786]

A cDNA clone (DNA77648-1688) encoding a native human PRO1605 polypeptide was identified by a yeast screen, in a human fetal kidney cDNA library that preferentially represents the 5' ends of the primary cDNA clones.

The full-length DNA77648-1688 clone shown in Figure 69 (SEQ ID NO:69) contains a single open

reading frame with an apparent translational initiation site at nucleotide positions 425-427 and ending at the stop codon at nucleotide positions 845-847 (Figure 69). The predicted polypeptide precursor is 140 amino acids long (Figure 70; SEQ ID NO:70). The full-length PRO1605 protein shown in Figure 70 has an estimated molecular weight of about 15,668 daltons and a pI of about 10.14. Analysis of the full-length PRO1605 sequence shown in Figure 70 (SEQ ID NO:70) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 26. Clone DNA77648-1688 has been deposited with ATCC on October 27, 1998 and is assigned ATCC deposit no. 203408.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 70 (SEQ ID NO:70), evidenced significant homology between the PRO1605 amino acid sequence and the following Dayhoff sequences: GNT5_HUMAN, P_R48975, P_W22519, MM26SPROT_1, HSU86782_1, CH60_LEPIN, HMCT_HELPY, F65126, HIU08875_1 and P_R41724.

EXAMPLE 37: Isolation of cDNA clones Encoding Human PRO1693 Polypeptides [UNQ803]

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA38251. Based on the DNA38251 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1693.

PCR primers (forward and reverse) were synthesized:

forward PCR primer (38251.f1) 5'-CTGGGATCTGAACAGTTTCGGGGC-3' (SEQ ID NO:208)
reverse PCR primer (38251.r1) 5'-GGTCCCCAGGACATGGTCTGTCCC-3' (SEQ ID NO:209)
Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA38251 sequence which had the following nucleotide sequence.

hybridization probe (38251.p1)

5'-GCTGAGTTTACATTTACGGTCTAACTCCCTGAGAACCATCCCTGTGCG-3' (SEQ ID NO:210)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1693 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1693 (designated herein as DNA77301-1708 [Figure 71, SEQ ID NO:71]; and the derived protein sequence for PRO1693.

The entire nucleotide sequence of DNA77301-1708 is shown in Figure 71 (SEQ ID NO:71). Clone DNA77301-1708 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 508-510 and ending at the stop codon at nucleotide positions 2047-2049 (Figure 71). The predicted polypeptide precursor is 513 amino acids long (Figure 72; SEQ ID NO:72). The full-length PRO1693 protein shown in Figure 72 has an estimated molecular weight of about 58,266 daltons and a pI of about 9.84. Analysis of the full-length PRO1693 sequence shown in Figure 72 (SEQ ID NO:72) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 33, a transmembrane domain from about

amino acid 420 to about amino acid 442, potential N-glycosylation sites from about amino acid 126 to about amino acid 129, from about amino acid 357 to about amino acid 360, from about amino acid 496 to about amino acid 499 and from about amino acid 504 to about amino acid 507, a cAMP- and cGMP-dependent protein kinase phosphorylation site from about amino acid 465 to about amino acid 468, a tyrosine kinase phosphorylation site from about amino acid 136 to about amino acid 142 and potential N-myristolation sites from about amino acid 11 to about amino acid 16, from about amino acid 33 to about amino acid 38, from about amino acid 245 to about amino acid 250, from about amino acid 332 to about amino acid 337, from about amino acid 497 to about amino acid 502 and from about amino acid 507 to about amino acid 512. Clone DNA77301-1708 has been deposited with ATCC on October 27, 1998 and is assigned ATCC deposit no. 203407.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 72 (SEQ ID NO:72), evidenced significant homology between the PRO1693 amino acid sequence and the following Dayhoff sequences: AB007876_1, ALS_MOUSE, HSCHON03_1, P_R85889, AF062006_1, AB014462_1, A58532, MUSLRRPA_1, AB007865_1 and AF030435_1.

EXAMPLE 38: Isolation of cDNA clones Encoding Human PRO1753 Polypeptides [UNQ826]

DNA68883 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST cluster sequence from the LIFESEQ® database, designated Incyte Cluster No. 54463. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence is herein designated "DNA54233". In light of the sequence homology between the DNA54233 sequence and EST no. 2597444, the EST clone 2597444 was purchased and the cDNA insert was obtained and sequenced in its entirety. EST clone 2597444 was derived from RNA isolated from ovarian tumor tissue. The sequence of this cDNA insert is shown in Figure 73 and is herein designated as "DNA68883-1691".

The full length clone shown in Figure 73 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 197 to 199 and ending at the stop codon found at nucleotide positions 1832 to 1834 (Figure 73; SEQ ID NO:73). The predicted polypeptide precursor (Figure 74, SEQ ID NO:74) is 545 amino acids long. PRO1753 has a calculated molecular weight of approximately 60022 daltons and an estimated pI of approximately 5.50. Additional features of PRO1753 include: a signal peptide at about amino acids 1-16; potential N-glycosylation sites at about amino acids 89-92, 116-119, 259-262, 291-294, and 299-302; potential tyrosine kinase phosphorylation sites at about amino acids 411-417 and 443-450; potential N-myristoylation sites at about amino acids 226-231, 233-238, 240-245, 252-257, 296-301, 300-305, 522-527, and 531-536; and an aspartic acid and asparagine hydroxylation site at about amino acids 197-208.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 74 (SEQ ID NO:74), revealed significant homology between the PRO1753 amino acid sequence and Dayhoff sequence MMU72678_1. Homology was also revealed between the PRO1753 amino acid sequence and the following additional the following Dayhoff sequences: GP2_HUMAN; UROM_HUMAN; MMU69262_1; P_W52840; EGF_HUMAN; P_P50296; P_W31705; CET05A1_8; and HSAJ474_1.

Clone DNA68883 (UNQ826), designated as DNA68883-1691 was deposited with the ATCC on December 15, 1998 and is assigned ATCC deposit no. 203535.

EXAMPLE 39: Isolation of cDNA clones Encoding Human PRO1755 Polypeptides [UNQ828]

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, designated EST Cluster No. 141872. This EST cluster sequence was then compared to a variety of ESTs from the databases listed above to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated "DNA55731".

In light of the sequence homology between the DNA55731 sequence and a sequence contained within Incyte EST no. 257323, the EST clone was purchased and the cDNA insert was obtained and sequenced. Incyte clone 257323 was derived from a library constructed using RNA isolated from the hNT2 cell line (Stratagene library no. STR9372310), which was derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor at an early stage of development. The sequence of this cDNA insert is shown in Figure 75 and is herein designated "DNA76396-1698". Alternatively, the DNA76396-1698 sequence can be obtained by preparing oligonucleotide probes and primers and isolating the sequence from an appropriate library (e.g. STR9372310).

The full length clone shown in Figure 75 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 58 to 60 and ending at the stop codon found at nucleotide positions 886 to 888 (Figure 75; SEQ ID NO:75). The predicted polypeptide precursor (Figure 76, SEQ ID NO:76) is 276 amino acids long. PRO1755 has a calculated molecular weight of approximately 29,426 daltons

and an estimated pI of approximately 9.40. Additional features include: a signal peptide sequence at about amino acids 1-31; a transmembrane domain at about amino acids 178-198; a cAMP and cGMP-dependent protein kinase phosphorylation site at about amino acids 210-213; potential N-myristoylation sites at about amino acids 117-122, 154-149, and 214-219; and a cell attachment sequence at about amino acids 149-151.

5 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 76 (SEQ ID NO:76), revealed some homology between the PRO1755 amino acid sequence and the following Dayhoff sequences: APG-BRANA, P_R37743, NAU88587_1, YHL1_EBV, P_W31855, CET10B10_4, AF039404_1, PRP1_HUMAN, AF038575_1, and AF053091_1.

10 Clone DNA76396-1698 was deposited with the ATCC on November 17, 1998, and is assigned ATCC deposit no. 203471.

EXAMPLE 40: Isolation of cDNA clones Encoding Human PRO1777 Polypeptides [UNQ8391]

15 The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public EST databases (e.g., GenBank), and a proprietary EST database (LIFESeq®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

20 A consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is herein designated DNA47435.

Based on the DNA47435 consensus sequence oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1777. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer (47434.f1) 5'-CTGTTACACTGACGTGGCCCTCCC-3' (SEQ ID NO:211)

reverse PCR primer (47434.r1) 5'-CATTCTGACCCACGGGCCATTGTC-3' (SEQ ID NO:212)

35 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47435 sequence which had the following nucleotide sequence

hybridization probe (47434.p1)

5'-GTGGAGCAGCCGGTGAAGTTGAGCAGCCTTGCCAGAAAGTATGC-3' (SEQ ID NO:213)

RNA for construction of the cDNA libraries was isolated from human hippocampus tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1777 (designated herein as DNA71235-1706 [Figure 77, SEQ ID NO: 77]; (UNQ839) and the derived protein sequence for PRO1777.

The entire nucleotide sequence of UNQ839 (DNA71235-1706) is shown in Figure 77 (SEQ ID NO:77). Clone UNQ839 (DNA71235-1706) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 797-799 and ending at the stop codon at nucleotide positions 2372-2374 (Figure 77). The predicted polypeptide precursor is 525 amino acids long (Figure 78; SEQ ID NO:78). The full-length PRO1777 protein shown in Figure 78 has an estimated molecular weight of about 57,133 daltons and a pI of about 6.55. Analysis of the full-length PRO1777 sequence shown in Figure 78 (SEQ ID NO:78) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 16, a transmembrane domain from about amino acid 353 to about amino acid 373, potential N-glycosylation sites from about amino acid 117 to about amino acid 120, from about amino acid 215 to about amino acid 218, from about amino acid 356 to about amino acid 359 and from about amino acid 497 to about amino acid 500, potential N-myristoylation sites from about amino acid 12 to about amino acid 17, from about amino acid 33 to about amino acid 38, from about amino acid 52 to about amino acid 57, from about amino acid 97 to about amino acid 102, from about amino acid 101 to about amino acid 106, from about amino acid 113 to about amino acid 118, from about amino acid 158 to about amino acid 163, from about amino acid 328 to about amino acid 333, from about amino acid 388 to about amino acid 393, from about amino acid 418 to about amino acid 423, from about amino acid 435 to about amino acid 440 and from about amino acid 436 to about amino acid 441, an amidation site from about amino acid 382 to about amino acid 385 and a sulfatase signature 2 sequence from about amino acid 129 to about amino acid 138. Clone UNQ839 (DNA71235-1706) has been deposited with ATCC on January 12, 1999 and is assigned ATCC deposit no. 203584.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 78 (SEQ ID NO:78), evidenced significant homology between the PRO1777 amino acid sequence and the following Dayhoff sequences: G02857, GA6S_HUMAN, HGS_A139, GEN12647, STS_HUMAN, GEN12648, SPHM_HUMAN, P_W47298, GEN13892 and AF050145_1.

EXAMPLE 41: Isolation of cDNA clones Encoding Human PRO1788 Polypeptides [UNQ850]

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2

[Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Incyte Clone No. 2968304 was identified as a sequence of interest having a BLAST score of 70 or greater that did not encode known proteins. The nucleotide sequence of Incyte Clone No. 2968304 is designated herein as "DNA6612".

In addition, the DNA6612 sequence was extended using repeated cycles of BLAST and phrap (Phil Green, University of Washington, Seattle, Washington) to extend the sequence as far as possible using the sources of EST sequences discussed above. The extended consensus sequence is designated herein as "DNA49648". Based on the DNA49648 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1788.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: CCCTGCCAGCCGAGAGCTTCACC (49648.f1; SEQ ID NO:214)

reverse PCR primer: GGTTGGTGCCCCGAAAGGTCCAGC (49648.r1; SEQ ID NO:215)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA49648 sequence which had the following nucleotide sequence:

hybridization probe: CAACCCCAAGCTTAAC TGGGCAGGAGCTGAGGTGTTTTCAGGCC (49648.p1; SEQ ID NO:216)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1788 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1788 (designated herein as DNA77652-2505 [Figure 79, SEQ ID NO:79]; and the derived protein sequence for PRO1788.

The entire coding sequence of DNA77652-2505 is shown in Figure 79 (SEQ ID NO:79). Clone DNA77652-2505 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 64-66 and an apparent stop codon at nucleotide positions 1123-1125. The predicted polypeptide precursor is 353 amino acids long (Figure 80; SEQ ID NO:80). The full-length PRO1788 protein shown in Figure 80 has an estimated molecular weight of about 37,847 daltons and a pI of about 6.80. Additional features of PRO1788 include: a signal peptide at about amino acids 1-16; transmembrane domains at about amino acids 215-232 and 287-304; potential N-glycosylation sites at about amino acids 74-77 and 137-140; a glycosaminoglycan attachment site at about amino acids 45-48; a tyrosine kinase phosphorylation site at about amino acids 318-325; N-myristoylation sites at about amino acids 13-18, 32-37, 88-93, 214-219, and 223-228; and a leucine zipper pattern at about amino acids 284-305.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 80 (SEQ ID NO:80), revealed significant homology between the PRO1788 amino acid sequence and the following Dayhoff sequences: AF030435_1; AF062006_1; DMTARTAN_1; GARP_HUMAN; S42799; P_R71294; HSU88879_1; DROWHEELER_1; A58532; and AF068920_1.

Clone DNA77652-2505 was deposited with the ATCC on November 17, 1998, and is assigned ATCC deposit no. 203480.

EXAMPLE 42: Isolation of cDNA clones Encoding Human PRO1864 Polypeptides [UNQ855]

5 The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public EST databases (e.g., GenBank), a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), and proprietary ESTs from Genentech. The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons
10 resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

A consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is herein designated Concen1424. In addition, the Consen1424 consensus DNA sequence was extended
15 using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above. The extended consensus sequence is herein designated DNA40649.

Based on the DNA40649 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1864. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and
20 are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe
25 oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer (40649.f1) 5'-CTCCTCCAGGATGAACCACTGCC-3' (SEQ ID NO:217)

forward PCR primer (40649.f2) 5'-CAGGATGCTTCAGAGAGG-3' (SEQ ID NO:218)

reverse PCR primer (40649.r1) 5'-CCTGCCTTCGGATTCCAGGAGGGG-3' (SEQ ID NO:219)

30 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40649 sequence which had the following nucleotide sequence
hybridization probe (40649.p1)

5'-CCATCAACCCACACAACCTCATGGCCAGGATTGAGTCCTATG-3' (SEQ ID NO:220)

RNA for construction of the cDNA libraries was isolated from human fetal liver tissue. The cDNA
35 libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor

of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1864 (designated herein as DNA45409-2511 [Figure 81, SEQ ID NO: 81]; (UNQ855) and the derived protein sequence for PRO1864.

5 The entire nucleotide sequence of UNQ855 (DNA45409-2511) is shown in Figure 81 (SEQ ID NO:81). Clone UNQ855 (DNA45409-2511) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 100-102 and ending at the stop codon at nucleotide positions 802-804 (Figure 81). The predicted polypeptide precursor is 234 amino acids long (Figure 82; SEQ ID NO:82). The full-length PRO1864 protein shown in Figure 82 has an estimated molecular weight of about 26,655 daltons and a pI of about 4.79.

10 Analysis of the full-length PRO1864 sequence shown in Figure 82 (SEQ ID NO:82) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20 and transmembrane domains from about amino acid 54 to about amino acid 72, from about amino acid 100 to about amino acid 118, from about amino acid 130 to about amino acid 144 and from about amino acid 146 to about amino acid 166. Clone UNQ855 (DNA45409-2511) has been deposited with ATCC on January 12, 1999 and is assigned ATCC deposit no. 203579.

15 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 82 (SEQ ID NO:82), evidenced significant homology between the PRO1864 amino acid sequence and the following Dayhoff sequences: P_W25768, I38027, D38255_1, MMES64_1, OCU92812_1, DRPATCH_1, DPOD_PLAFK, RTM1_YEAST, P_R77844 and P_R90765.

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EXAMPLE 43: Isolation of cDNA clones Encoding Human PRO1925 Polypeptides [UNQ904]

DNA82302 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon expressed sequence tags (ESTs) as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to

25 determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

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Use of the above described signal sequence algorithm allowed identification of an EST cluster sequence from the LIFESEQ® database, designated cluster sequence no. 31113_2. This EST cluster sequence was then compared to the EST databases listed above to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green,

35

University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated "DNA73884". In light of the sequence homology between the DNA73884 sequence and EST no. 3271608HI from the LIFESEQ® database, EST clone no. 3271608HI was purchased and the cDNA insert was obtained and sequenced. The clone originated from a library constructed using diseased human brain tissue. The sequence of this cDNA insert is shown in Figure 83 and is herein designated as DNA82302.

The full length clone shown in Figure 83 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 89 to 91 and ending at the stop codon found at nucleotide positions 1409 to 1411 (Figure 83; SEQ ID NO:83). The predicted polypeptide precursor (Figure 84, SEQ ID NO:84) is 440 amino acids long. PRO1925 has a calculated molecular weight of approximately 49,403 daltons and an estimated pI of approximately 7.16. Additional features include a type II transmembrane domain at about amino acids 39-56; tyrosine kinase phosphorylation sites at about amino acids 149-155 and 274-281; N-myristoylation sites at about amino acids 10-15, 20-25, 63-68, and 208-213; an amidation site at about amino acids 10-13; and a glycoprotein hormones beta chain signature 1 at about amino acids 230-236.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 84 (SEQ ID NO:84), revealed some homology between the PRO1925 amino acid sequence and the following Dayhoff sequences: P_R95913, AF010144_1, HSAF000996_1, HUMTRRP_1, P_W00838, I54374, PVPVA1_1, REL_HUMAN, HSU94362_1, and P_W19943.

Clone DNA82302 (UNQ904), designated as DNA82302-2529 was deposited with the ATCC on December 15, 1998 and is assigned ATCC deposit no. 203534.

EXAMPLE 44: Isolation of cDNA clones Encoding Human PRO1926 Polypeptides [UNQ905]

DNA82340 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

An EST sequence which was identified was then compared to a variety of ESTs from the databases mentioned above to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA73887.

In light of the sequence homology between the DNA73887 sequence and EST no. 3577105 from the LIFESEQ®, the EST clone, which was obtained from a cDNA library constructed from human bronchial tissue, was purchased and the cDNA insert was obtained and sequenced. The sequence of this cDNA insert is shown in Figure 85 and is herein designated "DNA82340-2530".

The full length clone shown in Figure 85 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 74 to 76 and ending at the stop codon found at nucleotide positions 800 to 802 (Figure 85; SEQ ID NO:85). The predicted polypeptide precursor (Figure 86, SEQ ID NO:86) is 242 amino acids long. PRO1926 has a calculated molecular weight of approximately 26,471 daltons and an estimated pI of approximately 9.50. Additional features include: a signal peptide at about amino acids 1-23; a transmembrane domain at about amino acids 136-180; a potential N-glycosylation site at about amino acids 184-187; glycosaminoglycan attachment sites at about amino acids 37-40 and 236-239; a cAMP- and cGMP-dependent protein kinase phosphorylation site at about amino acids 151-154; potential N-myristoylation sites at about amino acids 33-38, 36-41, 38-43, and 229-234; an amidation site at about amino acids 238-241; and an ATP/GTP binding site motif A (P-loop) at about amino acids 229-236.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 86 (SEQ ID NO:86), revealed 100 percent sequence identity between the last 81 carboxy terminus amino acids of the PRO1926 sequence and Dayhoff sequences P_W57893. Some homology was also found between the PRO1926 amino acid sequence and the following Dayhoff sequences: S72578, AR20_CAEEL, HGS_A198, HGS_A273, AF007570_1, GEN12401, DMSTKIN_1, FAT_DROME, MNB_DROME.

Clone DNA82340 (UNQ905), designated as DNA82340-2530 was deposited with the ATCC on December 22, 1998, and is assigned ATCC deposit no. 203547.

EXAMPLE 45: Isolation of cDNA clones Encoding Human PRO3566 Polypeptides [UNQ1840]

DNA59844-2542 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was

performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56016. In light of the sequence homology between the DNA56016 sequence and the Incyte EST clone no. 2603392, the Incyte EST clone no. 2603392 was purchased and the cDNA insert was obtained and sequenced. The sequence of this cDNA insert is shown in Figure 87 and is herein designated as DNA59844-2542.

Clone UNQ1840 (DNA59844-2542) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 5-7 and ending at the stop codon at nucleotide positions 980-982 (Figure 87; SEQ ID NO:87). The predicted polypeptide precursor is 325 amino acids long (Figure 88; SEQ ID NO:88). The full-length PRO3566 protein shown in Figure 88 has an estimated molecular weight of about 34,256 daltons and a pI of about 7.14. Analysis of the full-length PRO3566 sequence shown in Figure 88 (SEQ ID NO:88) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 26, and various other regions shown in Figure 88. Clone UNQ1840 (DNA59844-2542) has been deposited with ATCC on February 9, 1999 and is assigned ATCC deposit no. 203650.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 88 (SEQ ID NO:88), evidenced significant homology between the PRO3566 amino acid sequence and the following Dayhoff sequences: HELWAMIDE_1, CA21_MOUSE, SP62_HUMAN, AF095464_1, HMU92813_1, PRIO_BOVIN, SN24_HUMAN, TPM4_DROME, SYN1_RAT and CELT28F2_7.

EXAMPLE 46: Isolation of cDNA clones Encoding Human PRO4330 Polypeptides [UNQ1886]

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST, 4287529H1, (SEQ ID NO:3, also referred to herein as DNA85538 or from DNA) was identified which showed homology to thrombospondin.

RNA for construction of cDNA libraries was isolated from human aortic endothelial cells. The cDNA libraries used to isolate the cDNA clones encoding human PRO4330 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

The human cDNA libraries (prepared as described above), were screened by hybridization with a synthetic oligonucleotide probe:

5'GGAGACATGTTTCGAATGGACAAGTGTCTC3' (forward, SEQ ID NO:221);
5'CTGGATCTTCACACACTGGGCAGC3' (reverse, SEQ ID NO:222); and
5'CCCAGTGTGGTGAGATAAACTGCGAGAGCTACTACGTGCCCGAAGG3' (plasmid, SEQ ID NO:223).

A cDNA clone was sequenced in entirety. The entire nucleotide sequence including that coding PRO4330 is shown in Figure 89 (SEQ ID NO:89). Clone DNA90842-2574 contains a single open reading frame with an

apparent translational initiation site at nucleotide positions 368-370, and a stop codon at nucleotide positions 3476-3478 (Fig. 89; SEQ ID NO:89). The predicted polypeptide precursor is 1036 amino acids long (Figure 90; SEQ ID NO:90).

The full-length PRO4330 protein shown in Figure 90 has an estimated molecular weight of about 113738 daltons and a pI of about 5.14.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 90 (SEQ ID NO:90), revealed homology between the PRO4330 amino acid sequence and the following Dayhoff sequences (incorporated herein): D83017_1, P_W37500, NEL_RAT, P_W37501, NEL2_HUMAN, AF034606_1, P_W40288, CHRD_XENLA, TSP1_CHICK, and SOG_DROME.

EXAMPLE 47: Isolation of cDNA clones Encoding Human PRO4423 Polypeptides [UNQ1940]

DNA96893-2621 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST sequence from the Incyte database, a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). Based on DNA80594, DNA96893-2621 was identified and sequenced.

The full length clone shown in Figure 91 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 110-112 and ending at the stop codon found at nucleotide positions 639-641 (Figure 91; SEQ ID NO:91). The predicted polypeptide precursor (Figure 92, SEQ ID NO:92) is 173 amino acids long. PRO4423 has a calculated molecular weight of approximately 19733 daltons and an estimated pI of approximately 8.78.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 92 (SEQ ID NO:92), revealed homology between the PRO4423 amino acid sequence and the following Dayhoff sequences: S09646 and YHY4_YEAST.

Clone DNA96893-2621 (UNQ1940), designated as DNA96893-2621 was deposited with the ATCC on May 4, 1999 and is assigned ATCC deposit no. PTA-12.

EXAMPLE 48: Isolation of cDNA clones Encoding Human PRO4977 Polypeptides [UNQ2420]

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in

Example 1 above. Based on this consensus sequence, oligonucleotides were synthesized to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for PRO4977.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-ATGCCAATAACTTTGCCTCGGAGC-3' (SEQ ID NO:224)

5 reverse PCR primer 5'-CCAGAAGGCCAGGGCTTTCTCTG-3' (SEQ ID NO:225)

A hybridization probe was also synthesized:

5'-GAGTGCATGAGCAGCTGCCAGGGATCTCTCCATGGGCCCC-3' (SEQ ID NO:226)

10 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO4977 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from a human fetal kidney library. DNA sequencing of the clones isolated as described above gave the full-length DNA sequence and the derived protein sequence for PR4977.

15 The entire nucleotide sequence of DNA62849-2647 is shown in Figure 95 (SEQ ID NO:95). Clone DNA62849-2647 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 330-332, and an apparent stop codon at nucleotide positions 1761-1763. The predicted polypeptide precursor is 477 amino acids long (Figure 96; SEQ ID NO:96). Clone DNA62849-2647 has been deposited with ATCC on June 8, 1999 (designated as DNA62849-2647) and is assigned ATCC deposit no. PTA-205. The full-length PRO4977 protein has an estimated molecular weight of about 51112 daltons and a pI of about 6.66.

20 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 96 (SEQ ID NO:96), revealed homology between PTO4977 amino acid sequence and the following Dayhoff sequences: DJ534K4_3, AF41053_1, CELZK3777_2, AF060570_1, AF026465_1; I50600, HSU61262_1, DMU88578_1, P_W08747, and DMNRG2_2.

25 EXAMPLE 49: Isolation of cDNA clones Encoding Human PRO4980 Polypeptides [UNQ2422]

30 An initial DNA sequence, referred to herein as DNA81573 was identified by a yeast screen, in a human cDNA library that preferentially represents the 5' ends of the primary cDNA clones. This cDNA was then compared to ESTs from public databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. The ESTs were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA90613.

35 PCR primers (forward and reverse) were synthesized based upon the DNA90613 sequence for use as probes to isolate a clone of the full-length coding sequence for PRO4980 from a human aortic endothelial cell cDNA library:

forward PCR primer:

5'-CAACCGTATGGGACCGATACTCG-3' (SEQ ID NO:227)

reverse PCR primer:

5'-CACGCTCAACGAGTCTTCATG-3'

(SEQ ID NO:228)

hybridization probe:

5'-GTGGCCCTCGCAGTGCAGGCCTTCTACGTCCAATACAAGTG-3' (SEQ ID NO:229)

RNA for construction of the cDNA libraries was isolated from human aortic endothelial cell tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a Not I site, linked with blunt to Sal I hemikinased adaptors, cleaved with Not I, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the Sfi I site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique Xho I and Not I sites.

The full-length DNA97003-2649 clone obtained from this screen is shown in Figure 99 [SEQ ID NO:99] and contains a single open reading frame with an apparent translational initiation site at nucleotide positions 286-288, and an apparent stop codon at nucleotide positions 1900-1902. The predicted polypeptide precursor is 538 amino acids long (Figure 100; SEQ ID NO:100). The full-length PRO4980 protein shown in Figure 100 has an estimated molecular weight of about 59,268 daltons and a pI of about 8.94. Analysis of the full-length PRO4980 sequence shown in Figure 100 (SEQ ID NO:100) evidences the presence of a variety of important polypeptide domains, wherein the locations given for those important polypeptide domains are approximate as described above. Analysis of the full-length PRO4980 polypeptide shown in Figure 100 evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 36; transmembrane domains from about amino acid 77 to about amino acid 95, from about amino acid 111 to about amino acid 133, from about amino acid 161 to about amino acid 184, from about amino acid 225 to about amino acid 248, from about amino acid 255 to about amino acid 273, from about amino acid 299 to about amino acid 314, from about amino acid 348 to about amino acid 373, from about amino acid 406 to about amino acid 421, from about amino acid 435 to about amino acid 456, and from about amino acid 480 to about amino acid 497; an N-glycosylation site from about amino acid 500 to about amino acid 504; a cAMP- and cGMP-dependent protein kinase phosphorylation site from about amino acid 321 to about amino acid 325; N-myristoylation sites from about amino acid 13 to about amino acid 19, from about amino acid 18 to about amino acid 24, from about amino acid 80 to about amino acid 86, from about amino acid 111 to about amino acid 117, from about amino acid 118 to about amino acid 124, from about amino acid 145 to about amino acid 151, from about amino acid 238 to about amino acid 244, from about amino acid 251 to about amino acid 257, from about amino acid 430 to about amino acid 436, from about amino acid 433 to about amino acid 439, from about amino acid 448 to about amino acid 454, from about amino acid 458 to about amino acid 464, from about amino acid 468 to about amino acid 474, from about amino acid 475 to about amino acid 481, from about amino acid 496 to about amino acid 502, and from about amino acid 508 to about amino acid 514; and a prokaryotic membrane lipoprotein lipid attachment site from about amino acid 302 to about amino acid 313. Clone DNA97003-2649 has been deposited with the ATCC on May 11, 1999 and is assigned ATCC deposit no. PTA-43.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 100 (SEQ ID NO:100), evidenced significant homology between the PRO4980 amino acid sequence and the following Dayhoff sequences: SC59_YEAST,

S76857, CELF31F4_12, AC002464_1, NU5M_CHOCH, S59109, SAY10108_2, AF055482_2, F69049, and G70433.

EXAMPLE 50: Isolation of cDNA clones Encoding Human PRO4981 Polypeptides [UNQ2423]

5 A cDNA clone (DNA94849-2960) encoding a native human PRO4981 polypeptide was identified using a yeast screen, in a human Human testis cDNA library that preferentially represents the 5' ends of the primary cDNA clones.

10 Clone DNA94849-2960 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 145-147 and ending at the stop codon at nucleotide positions 1690-1692 (Figure 101; SEQ ID NO:101). The predicted polypeptide precursor is 515 amino acids long (Figure 102; SEQ ID NO:102). The full-length PRO4981 protein shown in Figure 102 has an estimated molecular weight of about 59357 daltons and a pI of about 9.40. Analysis of the full-length PRO4981 sequence shown in Figure 102 (SEQ ID NO:102) evidences the presence of a variety of important polypeptide domains as shown in Figure 102, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA94849-2960 has been deposited with ATCC on July 25, 2000 and is assigned ATCC deposit no. PTA-2306.

15 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 102 (SEQ ID NO:102), evidenced sequence identity between the PRO4981 amino acid sequence and the following Dayhoff sequences: TMA272073_1, AK001324_1, AE003806_12, AE003745_18, MS2_ARATH, AF149917_1, ATMS2LIPR_1, HETM_ANASP, T18552, LYS2_YEAST.

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EXAMPLE 51: Isolation of cDNA clones Encoding Human PRO5801 Polypeptides [UNQ2501]

25 The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included (1) public EST databases (e.g., GenBank) and (2) a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

30 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described above. This consensus sequence is herein designated DNA105850. In some cases, the consensus sequence derives from an intermediate consensus DNA sequence which was extended using repeated cycles of BLAST and phrap to extend that intermediate consensus sequence as far as possible using the sources of EST sequences discussed above.

35 Based on the DNA105850 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO5801. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55

bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

5 PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-ACTCCATATTTTCCTACTTGTGGCA-3' (SEQ ID NO:230)

forward PCR primer 2 5'-CCCAAAGTGACCTAAGAAC-3' (SEQ ID NO:231)

reverse PCR primer 5'-TCACTGAATTTCTTCAAACCATGCA-3' (SEQ ID NO:232)

10 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA105850 sequence which had the following nucleotide sequence

hybridization probe

5'-TGTGGCAGCGACTGCATCCGACATAAAGGAACAGTTGTGCTCTGCCCACA-3' (SEQ ID NO:233)

15 RNA for construction of the cDNA libraries was isolated from human fetal liver tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

20 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a full-length PRO5801 polypeptide (designated herein as DNA115291-2681 [Figure 103, SEQ ID NO: 103]) and the derived protein sequence for that PRO5801 polypeptide.

25 The full length clone identified above contained a single open reading frame with an apparent translational initiation site at nucleotide positions 7-9 and a stop signal at nucleotide positions 1513-1515 (Figure 103, SEQ ID NO:103). The predicted polypeptide precursor is 502 amino acids long, has a calculated molecular weight of approximately 55,884 daltons and an estimated pI of approximately 8.52. Analysis of the full-length PRO5801 sequence shown in Figure 104 (SEQ ID NO:104) evidences the presence of a variety of important polypeptide domains as shown in Figure 104, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA115291-2681 has been deposited with ATCC on June 8, 1999 and is assigned ATCC deposit no. PTA-202.

30 An analysis of the Dayhoff database shows that PRO5801 has sequence similarity to an IL-17 receptor protein and PRO5801 is also designated herein as IL-17RH1. Specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 104 (SEQ ID NO:104), evidenced sequence identity between the PRO5801 amino acid sequence and the following Dayhoff sequences: HSU58917_1, P_W92409, P_W61272, P_W04185, P_W61271, P_W04184, P_W92408, GEN13979, MMU31993_1 and YSO2_CAEL.

EXAMPLE 52: Isolation of cDNA clones Encoding Human PRO5995 Polypeptides [UNQ2507]

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included (1) public EST databases (e.g., Merck/Washington University) and (2) a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer
5 program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

10 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described above. This consensus sequence is herein designated DNA92934. In some cases, the DNA92934 consensus sequence derives from an intermediate consensus DNA sequence which was extended using repeated cycles of BLAST and phrap to extend that intermediate consensus sequence as far as possible using the sources of EST sequences discussed above.

15 Based on the DNA92934 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO5995. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater
20 than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:
25 forward PCR primer 5'GGATCTCTTGTTC AAGCATCCTACCAAC 3' (SEQ ID NO: 234)
reverse PCR primer 5'TGTCATCACTGCAAGTTAAGGCTTCCC 3' (SEQ ID NO: 235)
Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA92934 sequence which had the following nucleotide sequence
hybridization probe

30 5'CGTAGAGAAGTTATAATGCTGGCCTGCAGTTTTGGCAACAAGCACTG 3' (SEQ ID NO: 236)

RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis,
35 and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a

full-length PRO5995 polypeptide (designated herein as DNA96988-2685 [Figure 105, SEQ ID NO: 105]) and the derived protein sequence for that PRO5995 polypeptide.

The full length clone identified above contained a single open reading frame with an apparent translational initiation site at nucleotide positions 24-26 and a stop signal at nucleotide positions 3096-3098 (Figure 105, SEQ ID NO: 105). The predicted polypeptide precursor is 1024 amino acids long, has a calculated molecular weight of approximately 117049 daltons and an estimated pI of approximately 6.90. Analysis of the full-length PRO5995 sequence shown in Figure 106 (SEQ ID NO: 106) evidences the presence of a variety of important polypeptide domains as shown in Figure 106, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA96988-2685 has been deposited with ATCC on July 20, 1999 and is assigned ATCC Deposit No. PTA-384.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 106 (SEQ ID NO: 106), evidenced sequence identity between the PRO5995 amino acid sequence and the following Dayhoff sequences: I59331; AMPN_RAT; AMPN_HUMAN; AMPE_HUMAN; P_R94512; HUMPLAA_1; A65888_1; AAP1_YEAST; P_W33661; AF049234_1.

EXAMPLE 53: Isolation of cDNA clones Encoding Human PRO6095 Polypeptides [UNQ2543]

A cDNA clone (DNA105680-2710) encoding a native human PRO6095 polypeptide was identified using a yeast screen, in a human bone marrow cDNA library that preferentially represents the 5' ends of the primary cDNA clones.

Clone DNA105680-2710 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 372-374 and ending at the stop codon at nucleotide positions 458-460 (Figure 109; SEQ ID NO:109). The predicted polypeptide precursor is 457 amino acids long (Figure 110; SEQ ID NO:110). The full-length PRO6095 protein shown in Figure 110 has an estimated molecular weight of about 52,015 daltons and a pI of about 9.22. Analysis of the full-length PRO6095 sequence shown in Figure 110 (SEQ ID NO: 110) evidences the presence of a variety of important polypeptide domains as shown in Figure 110, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA105680-2710 has been deposited with ATCC on August 3, 1999 and is assigned ATCC Deposit No. PTA-483.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 110 (SEQ ID NO: 110), evidenced sequence identity between the PRO6095 amino acid sequence and the following Dayhoff sequences: CELZC328_5, F15K9_2, S59792, S78570, S53021, F1003_10, A57514, GAR2_SCHPO, A70387, and CELW09C3_4.

EXAMPLE 54: Isolation of cDNA clones Encoding Human PRO6182 Polypeptides [UNQ2553]

A cDNA clone (DNA110700-2716) encoding a native human PRO6182 polypeptide was identified using a yeast screen, in a human breast carcinoma cDNA library that preferentially represents the 5' ends of the primary cDNA clones.

Clone DNA110700-2716 contains a single open reading frame with an apparent translational initiation

site at nucleotide positions 18-20 and ending at the stop codon at nucleotide positions 1236-1238 (Figure 111; SEQ ID NO:111). The predicted polypeptide precursor is 406 amino acids long (Figure 112). The full-length PRO6182 protein shown in Figure 112 has an estimated molecular weight of about 43,878 daltons and a pI of about 6.50. Analysis of the full-length PRO6182 sequence shown in Figure 112 (SEQ ID NO: 112) evidences the presence of a variety of important polypeptide domains as shown in Figure 112, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA110700-2716 has been deposited with ATCC on August 10, 1999 and is assigned ATCC Deposit No. PTA-512.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 112 (SEQ ID NO: 112), evidenced sequence identity between the PRO6182 amino acid sequence and the following Dayhoff sequences: AB011161_1; AC005542_2; EMU41602_1; HUMIGCH06_1; PTN8_MOUSE; HUMIGCH08_1; AF012848_1; S17597; P_P40254; DTC_HUMAN.

EXAMPLE 55: Isolation of cDNA clones Encoding Human PRO7170 Polypeptides [UNO2782]

DNA108722-2743 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., Genbank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST cluster sequence from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, designated herein as CLU57836. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., Genbank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA58756.

In light of an observed sequence homology between the DNA58756 sequence and an EST sequence encompassed within clone no. 2251462 from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, CA, clone no. 2251462 was purchased and the cDNA insert was obtained and sequenced. It was found herein that that cDNA insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 113 and is herein designated as DNA108722-2743.

Clone DNA108722-2743 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 60-62 and ending at the stop codon at nucleotide positions 1506-1508 (Figure 113; SEQ ID NO:113). The predicted polypeptide precursor is 482 amino acids long (Figure 114; SEQ ID NO:114). The full-length PRO7170 protein shown in Figure 114 has an estimated molecular weight of about 49,060 daltons and a pI of about 4.74. Analysis of the full-length PRO7170 sequence shown in Figure 114 (SEQ ID NO: 114) evidences the presence of a variety of important polypeptide domains as shown in Figure 114, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA108722-2743 has been deposited with ATCC on August 17, 1999 and is assigned ATCC Deposit No. PTA-552.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 114 (SEQ ID NO: 114), evidenced sequence identity between the PRO7170 amino acid sequence and the following Dayhoff sequences: P_Y12291, I47141, D88733_1, DMC56G7_1, P_Y11606, HWP1_CANAL, HSMUC5BEX_1, HSU78550_1, HSU70136_1, and SGS3_DROME

EXAMPLE 56: Isolation of cDNA clones Encoding Human PRO7171 Polypeptides [UNQ2783]

DNA108670-2744 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., Genbank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST sequence from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, CA, designated herein as 212369. This EST sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., Genbank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA79089.

In light of an observed sequence homology between the DNA79089 sequence and an EST sequence encompassed within clone no. 212369 from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, CA, clone no.212369 was purchased and the cDNA insert was obtained and sequenced. It was found herein that that

cDNA insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 115 and is herein designated as DNA108670-2744.

Clone DNA108670-2744 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 93-95 and ending at the stop codon at nucleotide positions 495-497 (Figure 115; SEQ ID NO:115). The predicted polypeptide precursor is 134 amino acids long (Figure 116; SEQ ID NO:116). The full-length PRO7171 protein shown in Figure 116 has an estimated molecular weight of about 14,120 daltons and a pI of about 4.77. Analysis of the full-length PRO7171 sequence shown in Figure 116 (SEQ ID NO: 116) evidences the presence of a variety of important polypeptide domains as shown in Figure 116, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA108670-2744 has been deposited with ATCC on August 17, 1999 and is assigned ATCC Deposit No. PTA-546.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 116 (SEQ ID NO: 116), evidenced sequence identity between the PRO7171 amino acid sequence and the following Dayhoff sequences: AC007504_28, AF103900_1, OPUD_BACSU, G69670, T02361, and TS11_GIALA.

EXAMPLE 57: Isolation of cDNA clones Encoding Human PRO7436 Polypeptides [UNQ2973]

DNA119535-2756 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., Genbank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST sequence from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, CA, designated herein as 5325636. This EST sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., Genbank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA105428.

In light of an observed sequence homology between the DNA105428 sequence and an EST sequence encompassed within clone no. 5325636 from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, CA,

clone no.5325636 was purchased and the cDNA insert was obtained and sequenced. It was found herein that that cDNA insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 117 and is herein designated as DNA119535-2756.

Clone DNA119535-2756 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 211-213 and ending at the stop codon at nucleotide positions 1111-1113 (Figure 117; SEQ ID NO:117). The predicted polypeptide precursor is 300 amino acids long (Figure 118; SEQ ID NO:118). The full-length PRO7436 protein shown in Figure 118 has an estimated molecular weight of about 32,638 daltons and a pI of about 6.02. Analysis of the full-length PRO7436 sequence shown in Figure 118 (SEQ ID NO: 118) evidences the presence of a variety of important polypeptide domains as shown in Figure 118, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA119535-2756 has been deposited with ATCC on August 31, 1999 and is assigned ATCC Deposit No. PTA-613.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 118 (SEQ ID NO: 118), evidenced sequence identity between the PRO7436 amino acid sequence and the following Dayhoff sequences: AC005955_1, CGM1_HUMAN, P_R22041, CCEM_HUMAN, P_R06434, P_P93996, CE10_MOUSE, HOM6PSG2_1, PSG6_HUMAN, and ECTO_RAT.

EXAMPLE 58: Isolation of cDNA clones Encoding Human PRO9912 Polypeptides [UNQ3077]

An expressed sequence tag (EST) DNA database LIFESEQ (Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to autotaxin.

EST clone no. 2921845 was then purchased from LIFESEQ (Incyte Pharmaceuticals, Palo Alto, CA) and the cDNA insert of that clone was obtained and sequenced in entirety. The entire nucleotide sequence of the clone, designated herein as DNA108700-2802, is shown in Figure 119 (SEQ ID NO: 119). The DNA108700-2802 clone contains a single open reading frame with an apparent translational initiation site at nucleotide positions 4-6 and a stop signal at nucleotide positions 1378-1380 (Figure 119, SEQ ID NO:119). The predicted polypeptide precursor is 458 amino acids long, has a calculated molecular weight of approximately 51506 daltons and an estimated pI of approximately 6.79. Analysis of the full-length PRO9912 sequence shown in Figure 120 (SEQ ID NO:120) evidences the presence of a variety of important polypeptide domains as shown in Figure 120, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA108700-2802 has been deposited with ATCC on December 22, 1999 and is assigned ATCC deposit no. PTA-1093.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 120 (SEQ ID NO:120), evidenced sequence identity between the PRO9912 amino acid sequence and the following Dayhoff sequences: HS8B1_1, P_W75859, AB020686_1, P_Y17529, P_Y34324, T09933, PDNP3_1, PC1_HUMAN, HUMATXT_1 and P_R86595.

EXAMPLE 59: Isolation of cDNA clones Encoding Human PRO9917 Polypeptides [UNQ3079]

An expressed sequence tag (EST) DNA database LIFESEQ (Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to a human prostate stem cell antigen.

EST clone no. 2498349 was then purchased from Incyte Pharmaceuticals, Palo Alto, CA, and the cDNA insert of that clone was obtained and sequenced in entirety.

The entire nucleotide sequence of the clone, designated herein as DNA119474-2803, is shown in Figure 121 (SEQ ID NO: 121). The DNA119474-2803 clone contains a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and a stop signal at nucleotide positions 544-546 (Figure 121, SEQ ID NO:121). The predicted polypeptide precursor is 141 amino acids long, has a calculated molecular weight of approximately 15240 daltons and an estimated pI of approximately 8.47. Analysis of the full-length PRO9917 sequence shown in Figure 122 (SEQ ID NO:122) evidences the presence of a variety of important polypeptide domains as shown in Figure 122, wherein the locations given for those important polypeptide domains are approximate as described above. Chromosome mapping evidences that the PRO9917-encoding nucleic acid maps to 2q21-q22 in humans. Clone DNA119474-2803 has been deposited with ATCC on December 22, 1999 and is assigned ATCC deposit no. PTA-1097.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 122 (SEQ ID NO:122), evidenced sequence identity between the PRO9917 amino acid sequence and the following Dayhoff sequences: PSCA_1, P_W80956, AF043498_1, P_W70522, P_W86024, P_W62066, P_Y13938, P_Y13347, D45835 and HSU08839_1. Interestingly, the PRO9917 polypeptide lacks the GPI tail that almost all members of the Prostate Stem Cell Antigen (PSCA) family have.

EXAMPLE 60: Isolation of cDNA clones Encoding Human PRO19646 Polypeptides [UNQ5827]

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included (1) public EST databases (e.g., GenBank), (2) a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), (3) a proprietary EST database from Genentech. The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described above. This consensus sequence is herein designated DNA144267. In some cases, the consensus sequence derives from an intermediate consensus DNA sequence which was extended using repeated cycles of BLAST and phrap to extend that intermediate consensus sequence as far as possible using the sources of EST sequences discussed above.

Based on the DNA144267 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO19646. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater

than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

5 forward PCR primer 5' -- 3' (SEQ ID NO:237) GTCGCCCCATTCCTGCAACAG

reverse PCR primer 5' -- 3' (SEQ ID NO:238) GGGCCTGCTCTCCCTCTGAAGC

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA144267 sequence which had the following nucleotide sequence
hybridization probe

10 5' -- 3' (SEQ ID NO:239) GTGCTGGGCTCTGGAGCCACACTGCGTCTTCCGTC

RNA for construction of the cDNA libraries was isolated from human [identify tissue type] tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRK5B or pRK5D; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

20 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a full-length PRO19646 polypeptide (designated herein as DNA145841-2868 [Figure 127, SEQ ID NO: 127]) and the derived protein sequence for that PRO19646 polypeptide.

25 The full length clone identified above contained a single open reading frame with an apparent translational initiation site at nucleotide positions 199-201 and a stop signal at nucleotide positions 2322-2324 (Figure 127, SEQ ID NO:127). The predicted polypeptide precursor is 708 amino acids long, has a calculated molecular weight of approximately 75093 daltons and an estimated pI of approximately 6.65. Analysis of the full-length PRO19646 sequence shown in Figure 128 (SEQ ID NO:128) evidences the presence of a variety of important polypeptide domains as shown in Figure 128, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA145841-2868 has been deposited with ATCC on April 11, 2000 and is assigned ATCC deposit no. PTA-1678.

30 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 128 (SEQ ID NO:128), evidenced sequence identity between the PRO19646 amino acid sequence and the following Dayhoff sequences: DMC163A10_1, ICCR_DROME, NM_004646_1, AF210316_1, PGBM_HUMAN, NM_002821_1, P_W83927, HSU33G35_1, MAG_HUMAN, NM_001771_1.

35 EXAMPLE 61: Isolation of cDNA clones Encoding Human PRO19820 Polypeptides [UNQ5926]

DNA149911-2885 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon genomic DNA from public (e.g., GenBank) and/or private databases. In this instance, a genomic sequence from GenBank (Accession No:) was analyzed using the gene

prediction program GENSCAN, licensed from Stanford University. GENSCAN analysis predicts gene coding regions by identifying the potential exons and removing introns, creating DNA sequences which are then subjected to the signal algorithm. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. In order to determine whether the sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of a sequence from the GenBank database, designated herein as DNA144336.

Based on the DNA144336 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO19820. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:
forward PCR primer 5' - AGCCCCAGGGAGCACAGGCT- 3' (SEQ ID NO: 240)
reverse PCR primer 5' - GCTCGTCACGGCCATCTTCACC- 3' (SEQ ID NO: 241)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA144389 sequence which had the following nucleotide sequence
hybridization probe
5' - TGCGACAGCGGCATCAGGCGGTTCTTC - 3' (SEQ ID NO: 242)

RNA for construction of the cDNA libraries was isolated from human mixed tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRK5B or pRK5D; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a full-length PRO19820 polypeptide (designated herein as DNA149911-2885 [Figure 131, SEQ ID NO: 131]) and the derived protein sequence for that PRO19820 polypeptide.

Clone DNA149911-2885 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 9-11 and ending at the stop codon at nucleotide positions 342-344 (Figure 131). The

predicted polypeptide precursor is 111 amino acids long (Figure 132; SEQ ID NO:132). The full-length PRO19820 protein shown in Figure 132 has an estimated molecular weight of about 12447 daltons and a pI of about 8.31. Analysis of the full-length PRO19820 sequence shown in Figure 132 (SEQ ID NO:132) evidences the presence of a variety of important polypeptide domains as shown in Figure 132, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA149911-2885 has been deposited with ATCC on April 25, 2000 and is assigned ATCC deposit no. PTA-1776.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 132 (SEQ ID NO:132), evidenced sequence identity between the PRO19820 amino acid sequence and the following Dayhoff sequences: P_Y41705, NM_000727_1, G70864, CCG1_HUMAN, MNT_HUMAN, P_Y06527, T13049, P_W47524, AF030100_1, and RNAJ696_1.

EXAMPLE 62: Isolation of cDNA clones Encoding Human PRO21201 Polypeptides [UNQ6098].

DNA168028-2956 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon genomic DNA from public (e.g., GenBank) and/or private databases. In this instance, a genomic sequence from GenBank (Accession No: Z98200) was analyzed using the gene prediction program GENSCAN, licensed from Stanford University. GENSCAN analysis predicts gene coding regions by identifying the potential exons and removing introns, creating DNA sequences which are then subjected to the signal algorithm. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. In order to determine whether the sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of a sequence from the GenBank database, designated herein as DNA144330.

Based on the DNA144330 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO21201. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5' - TCCACGACCTCCTGTCGGAGC - 3' (SEQ ID NO: 243)

reverse PCR primer 5' - AGACCCTGTGCGGACTGCTGC - 3' (SEQ ID NO: 244)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA144330

sequence which had the following nucleotide sequence

hybridization probe 5' - AGCCCCGACCACAGCAGCAGCCCC - 3' (SEQ ID NO: 245)

RNA for construction of the cDNA libraries was isolated from a mixture of human tissues. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRK5B or pRK5D; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a full-length PRO21201 polypeptide (designated herein as DNA168028-2956 [Figure 133, SEQ ID NO: 133]) and the derived protein sequence for that PRO21201 polypeptide.

Clone DNA168028-2956 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 78-80 and ending at the stop codon at nucleotide positions 1080-1082 (Figure 133). The predicted polypeptide precursor is 334 amino acids long (Figure 134; SEQ ID NO:134). The full-length PRO21201 protein shown in Figure 134 has an estimated molecular weight of about 37257 daltons and a pI of about 5.95. Analysis of the full-length PRO21201 sequence shown in Figure 134 (SEQ ID NO:134) evidences the presence of a variety of important polypeptide domains as shown in Figure 134, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA168028-2956 has been deposited with ATCC on July 25, 2000 and is assigned ATCC deposit no. PTA-2304.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 134 (SEQ ID NO:134), evidenced sequence identity between the PRO21201 amino acid sequence and the following Dayhoff sequences: NM_014028_1, AF077205_1, YR53_CAEEL and T22084.

EXAMPLE 63: Isolation of cDNA clones Encoding Human PRO20026 Polypeptides [UNQ6115]

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described above. This consensus sequence is herein designated DNA149870. In some cases, the DNA149870 consensus sequence derives from an intermediate consensus DNA sequence which was extended using repeated cycles of BLAST and phrap to extend that intermediate consensus sequence as far as possible using the sources of EST sequences discussed above.

Based on the DNA149870 consensus sequence, flip cloning was performed. Oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO20026. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by Flip PCR amplification, as per Schanke et al., BioTechniques, 16:414-416 (1994), with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer:

5'-CGTTGTTTGTTCAGTGGAGAGCAGGG-3' (SEQ ID NO:246)

reverse PCR primer

5'-CAGGAACACCTGAGGCAGAAGCG -3' (SEQ ID NO: 247)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA149870 sequence which had the following nucleotide sequence

hybridization probe

5'-CTATCTCCCTGCCAGGAGGCCGGAGTGGGGGAGGTCAGAC-3' (SEQ ID NO: 248)

RNA for construction of the cDNA libraries was isolated from human tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a full-length PRO20026 polypeptide (designated herein as DNA154095-2998 [Figure 135, SEQ ID NO: 135]) and the derived protein sequence for that PRO20026 polypeptide.

The full length clone identified above contained a single open reading frame with an apparent translational initiation site at nucleotide positions 70-72 and a stop signal at nucleotide positions 2254-2256 (Figure 135, SEQ ID NO: 135). The predicted polypeptide precursor is 728 amino acids long, has a calculated molecular weight of approximately 81,310 daltons and an estimated pI of approximately 6.84. Analysis of the full-length PRO20026 sequence shown in Figure 136 (SEQ ID NO: 136) evidences the presence of a variety of important polypeptide domains as shown in Figure 136, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA154095-2998 has been deposited with ATCC on October 10, 2000 and is assigned ATCC Deposit No. PTA-2591.

An analysis of the Dayhoff database shows that PRO20026 has sequence similarity to an IL-17 receptor protein and PRO2006 is also designated herein as IL-17RH4. Specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown

in Figure 136 (SEQ ID NO: 136), evidenced sequence identity between the PRO20026 amino acid sequence and the following Dayhoff sequences: T42695, P_W04185, P_W92409, P_W61272, NM_014339_1, HSU58917_1, MMU31993_1, GEN13979, P_W04184, P_W61271.

EXAMPLE 64: Isolation of cDNA clones Encoding Human PRO23202 Polypeptides [UNQ6507]

5 An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified by GEPIS. Gene expression profiling in silico (GEPIS) is a bioinformatics tool that characterizes genes of interest for new therapeutic targets. GEPIS takes advantage of the vast amount of EST sequence and library information to determine gene expression profiles. GEPIS is based on the assumption that the expression level of a gene is proportionally correlated with the number of its occurrences in EST databases, and it works by integrating the Incyte EST relational database and Genentech proprietary information in a stringent and statistically meaningful way. In this example, it is used to identify and cross-validate new tumor antigens, although GEPIS can be configured to either perform very specific analyses or broad screening tasks. For the initial screen, GEPIS is used to go from libraries to sequence. The entire Incyte database was used to cluster sequence based on its library information. Breast, colon, lung and prostate were the target organs specified. The sequences found in this initial cluster were then subjected to a screen for secreted and transmembrane containing domains. The remaining sequences were then screened for novelty and those individual sequences identified. In a final step, each individual sequence was then put through a GEPIS screen, this time going from sequence to library, confirming its expression profile in the original target tissue. Using this type of screening bioinformatics, DNA182753 was identified, and PCR primers designed using this sequence were used to screen libraries for the full length clone.

15 RNA for construction of cDNA libraries was then isolated from human prostate tissue. The cDNA libraries used to isolate the cDNA clones encoding human PRO23203 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

25 Oligonucleotides probes based upon the above described EST sequence were then synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO23203. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

35 The oligonucleotide probes employed were as follows:
forward PCR primer 5'-GATATTTGTTTCTCAACATGGCTTATCAGCAGG-3' (SEQ ID NO:249)
reverse PCR primer 5'-TCTCTGACCTTCTCATCGGTAAGCAGAGG-3' (SEQ ID NO:250)

hybridization probe 5'-TCTTTTGCAGCTTTGCAGATACCCAGACTGAGCTGGAACTGGA-3' (SEQ ID NO:251)

A full length clone [herein designated DNA185171-2994] was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 188-190 and a stop signal at nucleotide positions 1550-1552 (Figure 139, SEQ ID NO:139). The predicted polypeptide precursor is 454 amino acids long, has a calculated molecular weight of approximately 52008 daltons and an estimated pI of approximately 8.83. Analysis of the full-length PRO23203 sequence shown in Figure 140 (SEQ ID NO:140) evidences the presence of a variety of important polypeptide domains as shown in Figure 140, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA185171-2994 has been deposited with ATCC on September 26, 2000 and is assigned ATCC deposit no. PTA-2513.

An analysis of the protein database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 140 (SEQ ID NO:140), evidenced sequence identity between the PRO23203 amino acid sequence and the following sequences:AK001691_1.

EXAMPLE 65: Isolation of cDNA clones Encoding Human PRO35250 Polypeptides [UNQ9574]

DNA171732-3100 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST sequence from the LIFESEQ® (Incyte Pharmaceuticals, Palo Alto, CA) database, designated herein as 248197.2. The source of the EST sequence was a library prepared from right temporal lobe tissue removed from a 45-year-old black male during a brain lobectomy. CDNA synthesis was initiated using a NotI-anchored oligo(dT) primer. Double-stranded cDNA was blunted, ligated to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte). This EST sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA130657.

In light of an observed sequence homology between the DNA130657 sequence and an EST sequence encompassed within clone no. 4028188 from the LIFESEQ® (Incyte Pharmaceuticals, Palo Alto, CA) database, clone no. 4028188 was purchased and the cDNA insert was obtained and sequenced. It was found herein that the cDNA insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 141 and is herein designated as DNA171732-3100.

5 Clone DNA171732-3100 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 52-54 and ending at the stop codon at nucleotide positions 604-606 (Figure 141; SEQ ID NO:141). The predicted polypeptide precursor is 184 amino acids long (Figure 142; SEQ ID NO:142). The full-length PRO35250 protein shown in Figure 142 has an estimated molecular weight of about 19,806 daltons and a pI of about 4.74. Analysis of the full-length PRO35250 sequence shown in Figure 142 (SEQ ID NO:142) evidences the presence of a variety of important polypeptide domains as shown in Figure 142, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA171732-3100 has been deposited with ATCC on April 24, 2001 and is assigned ATCC deposit no. PTA-3329.

15 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 142 (SEQ ID NO:142), evidenced sequence identity between the PRO35250 amino acid sequence and the following Dayhoff sequence: AK003305_1.

EXAMPLE 66: Generation and Analysis of Mice Comprising PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Gene Disruptions

To investigate the role of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides, disruptions in PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001,

PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 genes were produced by homologous recombination or retroviral insertion techniques. Specifically, transgenic mice comprising disruptions in PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 genes (i.e., knockout mice) were created by either gene targeting or gene trapping. Mutations were confirmed by southern blot analysis to confirm correct targeting on both the 5' and 3' ends. Gene-specific genotyping was also performed by genomic PCR to confirm the loss of the endogenous native transcript as demonstrated by RT-PCR using primers that anneal to exons flanking the site of insertion. Targeting vectors were electroporated into 129 strain ES cells and targeted clones were identified. Targeted clones were microinjected into host blastocysts to produce chimeras. Chimeras were bred with C57 animals to produce F1 heterozygotes. Heterozygotes were intercrossed to produce F2 wildtype, heterozygote and homozygote cohorts which were used for phenotypic analysis. Rarely, if not enough F1 heterozygotes were produced, the F1 hets were bred to wildtype C57 mice to produce sufficient heterozygotes to breed for cohorts to be analyzed for a phenotype. All phenotypic analysis was performed from 12-16 weeks after birth.

Overall Summary of Phenotypic Results:

66.1. Generation and Analysis of Mice Comprising DNA284870 (UNQ128) Gene Disruptions

In these knockout experiments, the gene encoding PRO69122 polypeptides (designated as DNA284870) (UNQ128) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: AK005023 Mus musculus adult male liver cDNA, RIKEN full-length enriched library, clone:1300016D21 product:Sel1 (suppressor of lin-12) 1 homolog (C. elegans); protein reference: Q9Z2G6 ACCESSION:Q9Z2G6 NID: Mus musculus (Mouse). Sel-1 homolog precursor (Suppressor of lin-12-like protein) (Sel-1L); the human gene sequence reference: NM_005065 ACCESSION:NM_005065 NID:19923668 Homo sapiens Homo sapiens sel-1 suppressor of lin-12-like (C. elegans) (SEL1L); the human protein sequence corresponds to reference: Q9UBV2 ACCESSION:Q9UBV2 NID: Homo sapiens (Human). SEL-1 HOMOLOG PRECURSOR (SUPPRESSOR OF LIN-12-LIKE PROTEIN) (SEL-1L).

The mouse gene of interest is Sel1h (Sel1 [suppressor of lin-12] 1 homolog [C. elegans]), ortholog of human SEL1L (sel-1 suppressor of lin-12-like [C. elegans]). Aliases include IBD2; SEL1-LIKE; sel-1 (suppressor of lin-12, C.elegans)-like; and Suppressor of lin 12 (sel-1), C. elegans, homolog of.

SEL1L is an intracellular vesicle-associated protein, consisting of a signal peptide, a fibronectin type II domain, a transmembrane segment, and a proline-rich C terminus. Although the function of this protein is unknown, SEL1L has been proposed to play a role in processes such as Notch signaling, intracellular protein

trafficking, secretion, cell growth inhibition, and tumor aggressiveness; the gene is expressed during pancreas development and in neural tube and dorsal root ganglia (Donoviel et al, Mech Dev 78(1-2):203-7 (1998); Cattaneo et al, Gene 326:149-56 (2004); Chiaramonte et al, Anticancer Res 22(6C):4211-4 (2002); Orlandi et al, Cancer Res 62(2):567-74 (2002); Biunno et al, Genomics 46(2):284-6 (1997); Grant and Greenwald, Development 124(3):637-44 (1997)).

- 5 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd} /C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I
- 10 phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	36	0	52
Expected	13.0	26.0	13.0	52

Chi-Sq.= 33.49 Significance= 5.3424262E-8 (hom/n)= 0.0 Avg. Litter Size= 8

- 15 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_011344.1).

Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

- 20 QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.1:1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA284870 (UNQ128))

(a) *OVERALL PHENOTYPIC SUMMARY:*

- 25 Mutation of the gene encoding the ortholog of human sel-1 suppressor of lin-12-like (C. elegans) (SEL1L) resulted in lethality of (-/-) mutants. Gene disruption was confirmed by Southern blot.

(b) *Microarray Analysis*

Tissue microarray analysis shows UNQ128 to be strongly expressed in the pancreas and down regulated in pancreatic carcinomas. In addition, UNQ128 is also overexpressed in breast tumors compared to normal breast tissue.

- 30 (c) *Pathology*

Microscopic: Not tested due to embryonic lethality. At 12.5 days, there were 40 embryos observed: 21(+/-) embryos, 2 (+/+) embryos, 4 resorption moles, 10 to-be-determined, and 3 inconclusive.

- Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemistry. Transverse sections of LacZ wholemounts in heterozygous embryos at 12.5 dpc shows expression in the inner layer of the
- 35 retina; forelimb muscle; endothelium of the cranial vasculature and floor plate expression in the neural tube which is indicative of a role in neural patterning.

Discussion related to embryonic developmental abnormality of lethality:

Embryonic lethality in knockout mice usually results from various serious developmental problems

including but not limited to neurodegenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

66.2. Generation and Analysis of Mice Comprising DNA30871-1157 (UNQ178) Gene Disruptions

In these knockout experiments, the gene encoding PRO204 polypeptides (designated as DNA30871-1157) (UNQ178) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019790 Mus musculus transmembrane protein with EGF-like and two follistatin-like domains 2 (Tmeff2); protein reference: Q9QYM9 ACCESSION:Q9QYM9 NID: Mus musculus (Mouse). TMEFF2 PROTEIN PRECURSOR; the human gene sequence reference: NM_016192 ACCESSION:NM_016192 NID:12383050 Homo sapiens Homo sapiens transmembrane protein with EGF-like and two follistatin-like domains 2 (TMEFF2); the human protein sequence corresponds to reference: Q9UIK5 ACCESSION:Q9UIK5 NID: Homo sapiens (Human). TMEFF2 PROTEIN PRECURSOR (TRANSMEMBRANE PROTEIN TENB2) (TPEF) (TRANSMEMBRANE PROTEIN WITH EGF-LIKE AND TWO FOLLISTATIN-LIKE DOMAINS 2).

The mouse gene of interest is Tmeff2 (transmembrane protein with EGF-like and two follistatin-like domains 2), ortholog of human TMEFF2. Aliases include 4832418D20Rik, TR, HPP1, TPEF, TENB2, tomoregulin, transmembrane protein TENB2, and putative transmembrane protein with EGF-like and two follistatin-like domains 2.

TMEFF2 is a type I plasma membrane protein that may function as a protease inhibitor or signal transducing receptor. The protein contains a signal peptide, two Kazal-type serine protease inhibitor domains (Pfam accession PF00050), an EGF-like domain, a transmembrane segment, and a cytoplasmic C-terminal G protein-activating motif. TMEFF2 undergoes ectodomain shedding to produce a secreted form, consisting of the protease domains and the EGF-like domain. The extracellular segment of TMEFF2 is capable of stimulating tyrosine phosphorylation of receptor tyrosine kinase ERBB4, suggesting that TMEFF2 functions as a signal-transducing ligand. Moreover, the TMEFF2 extracellular segment can increase survival of cultured neurons, suggesting that TMEFF2 functions as a survival factor. TMEFF2 gene is hypermethylated in several types of cancer, and ectopic TMEFF2 gene expression in prostate cancer cell lines inhibits growth, suggesting that TMEFF2 functions as a tumor suppressor. TMEFF2 is primarily expressed in distinct subsets of neurons in brain but is also expressed in colon, bladder, prostate, and several other tissues. A monoclonal antibody reactive with TMEFF2 and conjugated with the cytotoxic agent auristatin-E has been validated in mice as a treatment for prostate cancer (Uchida et al, Biochem Biophys Res Commun 266(2):593-602 (1999); Horie et al, Genomics 67(2):146-52 (2000); Liang et al, Cancer Res 60(17):4907-12 (2000); Lin et al, Life Sci 73(13):1617-27 (2003); Gery et al, Oncogene 21(31):4739-46 (2002); Gery and Koeffler, J Mol Biol 328(5):977-83 (2003); Afar et al, Mol Cancer Ther 3(8):921-32 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEvtm-derived embryonic stem (ES) cells.

The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

5		<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
	Observed	23	39	20	82
	Expected	20.5	41.0	20.5	82

Chi-Sq.= 1.02 Significance= 0.6004956 (hom/n)= 0.29 Avg. Litter Size= 8

Mutation Information

10 Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_019790.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

15

66.2.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA30871-1157 (UNQ178))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human transmembrane protein with EGF-like and two follistatin-like domains 2 (TMEFF2) resulted in small (-/-) mice that failed to thrive. The homozygous mutant mice were small and sickly, with several dying by 3 weeks of age. The remaining homozygous mutants were transferred to necropsy, where microscopic analysis revealed leukopenia and bone marrow hypoplasia. In addition, there was widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cell areas in the spleen. Leukopenia and bone marrow hypoplasia were noted in the (-/-) mice. Gene disruption was confirmed by Southern blot.

25

(b) *Pathology Assay-Specific Summary*

Gross: The homozygous mutant mice were small and failed to thrive, exhibiting body weights less than half that of normal age-matched wild-type mice. Most organs were small in proportion to reduced overall weight in the (-/-) mice. The spleen and thymus were especially reduced in size compared with the wildtype littermate controls.

Microscopic: The (-/-) mice exhibited leukopenia, due to both lymphopenia and granulocytopenia, and granulocytic hypoplasia of bone marrow. The bone marrow was diffusely hypoplastic in (-/-) mice, with normal amounts of erythropoiesis but markedly decreased numbers of myeloid granulocytic cell precursors, suggesting that decreased granulocytopenia caused the leukopenia. There was widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cell areas in the spleen. Thymic involution is a common finding in stressed or severely ill mice and often results in lymphopenia.

35 Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Bone Metabolism & Body Diagnostics*

(1) *Tissue Mass & Lean Body Mass Measurements - Dexa*

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type and 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Results: Obvious: The (-/-) mice were small and sickly, with several dying by 3 weeks of age. Of the surviving (-/-) mutants, 6 were transferred to necropsy at 3 weeks of age and the rest were euthanized for pathology at 3.5 weeks of age.

66.3. Generation and Analysis of Mice Comprising DNA32286-1191 (UNQ188) Gene Disruptions

In these knockout experiments, the gene encoding PRO214 polypeptides (designated as DNA32286-1191) (UNQ188) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_133930 ACCESSION:NM_133930 NID: gi 19527147 ref NM_133930.1 Mus musculus cysteine-rich with EGF-like domains 1 (Crel1); protein reference:Q91XD7 ACCESSION:Q91XD7 NID: Mus musculus (Mouse). UNKNOWN; the human gene sequence reference: NM_015513 ACCESSION:NM_015513 NID: gi 22095396 ref NM_015513.2 Homo sapiens cysteine-rich with EGF-like domains 1 (CRELD1); the human protein sequence corresponds to reference: Q9Y409 ACCESSION:Q9Y409 NID: Homo sapiens (Human). HYPOTHETICAL 44.9 KDA PROTEIN.

The mouse gene of interest is Crel1 (cysteine-rich with EGF-like domains 1), ortholog of human CRELD1. Aliases include AVSD2, CIRRN, DKFZP566D213, and atrioventricular septal defect 2. CRELD1 is a type III plasma membrane protein that may function as a cell adhesion molecule. The protein contains a signal peptide, a tryptophan- and glutamate-rich (WE) domain, a tandem array of EGF-like repeats, and two C-terminal transmembrane segments separated by a short cytoplasmic domain. Mutations in the CRELD1 gene may increase the risk of developing atrioventricular septal defect (Robinson et al, *Am J Hum Genet* 72(4):1047-52 (2003); Rupp et al, *Gene* 293(1-2):47-57 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	30	0	46
Expected	11.5	23.0	11.5	46

Chi-Sq.= 34.36 Significance= 3.4579656E-8 (hom/n)= 0.0 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_133930.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except adipose and stomach, small intestine, and colon.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

5

66.3.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA32286-1191 (UNQ188))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human cysteine-rich with EGF-like domains 1 (CRELD1) resulted in lethality of (-/-) mutants. Gene disruption was confirmed by Southern blot.

10

(b) *Pathology*

Microscopic: Not tested due to embryonic lethality. At 12.5 days, there were 50 embryos observed: 19 (+/-) embryos, 13 (++) embryos, 16 resorption moles, and 2 inconclusive.

Discussion related to embryonic developmental abnormality of lethality:

15

Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

20

UNQ188 deficient mice have heart defects and die about mid-gestation from cardiac insufficiency. *Ex vivo* analysis shows that UNQ188 is required for endothelial cell migration during heart development, defining the developmental pathway for UNQ188 function in the embryonic heart.

25

66.4. Generation and Analysis of Mice Comprising DNA33107-1135 (UNQ196) Gene Disruptions

In these knockout experiments, the gene encoding PRO222 polypeptides (designated as DNA33107-1135) (UNQ196) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_144796 Mus musculus RIKEN cDNA E430021N18 gene (E430021N18Rik); protein reference: Q8BH32 ACCESSION:Q8BH32 NID: Mus musculus (Mouse). Mus musculus 16 days neonate cerebellum cDNA, RIKEN full-length enriched library, clone:9630004A14 product:hypothetical Sushi domain / SCR repeat / CCP module containing protein, full insert sequence (Mus musculus 2 days neonate thymus thymic cells cDNA, RIKEN full-length enriched library, clone:E430021N18 product:hypothetical Sushi domain / SCR repeat / CCP module containing protein, full insert sequence); the human gene sequence reference: AY358495 Homo sapiens clone DNA33107 YHGM196 (UNQ196); the human protein sequence corresponds to reference: Q6UX62 ACCESSION:Q6UX62 NID: Homo sapiens (Human). YHGM196.

30

35

The mouse gene of interest is RIKEN cDNA E430021N18 gene, ortholog of human "clone DNA33107 YHGM196" (YHGM196). Aliases include MGC30368 and UNQ196.

YHGM196 is a putative type I plasma membrane protein, consisting of a signal peptide, four sushi

domains, a transmembrane segment, and a cytoplasmic C terminus. The function of this protein is not known; however, sushi domains are frequently found in cell adhesion molecules and complement (Pfam accession PF00084).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	14	43	19	76
Expected	19.0	38.0	19.0	76

Chi-Sq.= 0.04 Significance= 0.9801987 (hom/n)= 0.25 Avg. Litter Size= 9

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 (NCBI accession NM_144796.2) and the preceding noncoding exon (NCBI accession BM944003) were targeted.

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle; bone; and stomach, small intestine, and colon.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.4.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA33107-1135 (UNQ196))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human "clone DNA33107 YHGM196" (YHGM196) resulted in decreased systolic blood pressure in the (-/-) mice. In addition, the mutant (-/-) mice showed increased mean serum IgG3 levels compared with the control (+/+) littermates. Gene disruption was confirmed by Southern blot.

(b) *Microarray Analysis*

Microarray analysis reveals that UNQ196 is overexpressed or upregulated in breast cancer compared to normal breast tissue. In addition, UNQ196 is expressed in the embryonic mammary gland.

(c) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an

ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

The (-/-) mice exhibited increased mean serum IgG3 levels compared to their gender-matched (+/+) littermate controls, the (+/+) mice for the project run and the historical median.

The serum immunoglobulin isotyping assay revealed that homozygous adults exhibited increased serum IgG3 levels. Thus, homozygotes showed elevated serum immunoglobulins compared with the (+/+) littermates. IgG3 immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. These immunological abnormalities suggest that antagonists or inhibitors of PRO222 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised

patients, such as AIDS sufferers. Accordingly, PRO222 polypeptides or agonists thereof acting as a negative regulator would inhibit the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(d) *Cardiology - Blood Pressure*

Test Description: Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious systolic blood pressure.

Results

The (-/-) mice exhibited decreased mean systolic blood pressure (1 SD below the historic means) when compared with that of their gender-matched (+/+) littermates and the historical mean.

66.5. Generation and Analysis of Mice Comprising DNA35557-1137 (UNQ208) Gene Disruptions

In these knockout experiments, the gene encoding PRO234 polypeptides (designated as DNA3557-1137) (UNQ208) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: XM_146887 PREDICTED: Mus musculus RIKEN cDNA E030012M19 gene (E030012M19Rik); protein reference: XP_146887 similar to layilin [Mus musculus]; the human gene sequence reference: NM_178834 Homo sapiens layilin (LOC143903); the human protein sequence corresponds to reference: Q96NF3 ACCESSION:Q96NF3 NID: Homo sapiens (Human). CDNA FLJ30977 FIS, CLONE HHDPC2000095, HIGHLY SIMILAR TO CRICETULUS GRISEUS LAYILIN.

The mouse gene of interest is RIKEN cDNA E030012M19 gene, ortholog of human layilin. Aliases include Gm511.

Layilin is a type I integral plasma membrane protein that likely functions as a cell adhesion molecule or receptor. The protein binds with the extracellular matrix protein hyaluronan and associates with cytoskeletal adaptor protein talin. Layilin likely plays a role in processes such as cell adhesion, motility, and wound healing (Borowsky and Hynes, *J Cell Biol* 143(2):429-42 (1998); Bono et al, *Mol Biol Cell* 12(4):891-900 (2001)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	23	39	10	72
Expected	18	36	18	72

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 3 were targeted (NCBI accession XM_146887.3).

Chi-Sq.= 3.56 Significance= 0.16863815 (hom/n)= 0.23 Avg. Litter Size= 9

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.5.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA35557-1137 (UNQ208))

(a) *OVERALL PHENOTYPIC SUMMARY:*

5 Mutation of the gene encoding the ortholog of human layilin resulted in about half the expected numbers of homozygotes genotyped. The male (-/-) mice also exhibited decreased mean lean body mass. In addition, the male knockout mice showed decreased bone mineral content (BMC) and decreased bone mineral density (BMD) in total body, femurs, and vertebrae. Gene disruption was confirmed by Southern blot.

(b) *Bone Metabolism & Body Diagnostics/Radiology Phenotypic Analysis*

10 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:
 · DEXA for measurement of bone mineral density on femur and vertebra
 · MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

15 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

20 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

25 Mutant (-/-) mice deficient in the gene encoding PRO234 polypeptides show a phenotype consistent with tissue wasting diseases marked by decreased lean body mass. In addition, the male knockout mice showed decreased bone mineral content (BMC) and decreased bone mineral density (BMD) in total body, femurs and vertebrae. Thus, the (-/-) mice showed signs of tissue wasting disease and bone metabolism abnormalities which are commonly associated with osteoporosis. PRO234 polypeptides or agonists thereof would be useful for bone
 30 healing or for treating bone related disorders such as osteoporosis, whereas antagonists or inhibitors of PRO234 polypeptides would mimic the negative bone phenotype.

66.6. Generation and Analysis of Mice Comprising DNA36350-1158 (UNQ232) Gene Disruptions

35 In these knockout experiments, the gene encoding PRO265 polypeptides (designated as DNA36350-1158) (UNQ232) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_201518 Mus musculus fibronectin leucine rich transmembrane protein 2 (Flrt2); protein reference: Q8BLU0 ACCESSION:Q8BLU0 NID: Mus musculus (Mouse). Mus musculus adult male aorta and vein cDNA, RIKEN full-length enriched library, clone:A530098L04 product:KIAA0405

(LEUCINE-RICH REPEAT TRANSMEMBRANE PROTEIN FLRT2) homolog (Fibronectin leucine rich transmembrane protein 2); the human gene sequence reference: NM_013231 Homo sapiens fibronectin leucine rich transmembrane protein 2 (FLRT2); the human protein sequence corresponds to reference: O43155 ACCESSION:O43155 NID: Homo sapiens (Human). Leucine-rich repeat transmembrane protein FLRT2 precursor (Fibronectin-like domain-containing leucine-rich transmembrane protein 2) (UNQ232/PRO265).

5 The mouse gene of interest is Flrt2 (fibronectin leucine rich transmembrane protein 2), ortholog of human FLRT2. Aliases include KIAA0405.

FLRT2 is a putative type I plasma membrane protein expressed in pancreas, skeletal muscle, brain, and heart. The protein contains a signal peptide, several leucine-rich repeats, a fibronectin domain, a transmembrane segment, and a short cytoplasmic C terminus. FLRT2 is likely to function in receptor signaling (Lacy et al, Genomics 62(3):417-26 (1999); FLRT3 promotes neurite outgrowth and is upregulated upon nerve damage [Bottcher et al, Nat Cell Biol 6(1):38-44 (2004)].

10 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd} /C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	25	46	2	73
Expected	18.25	36.5	18.25	73

20 Chi-Sq.= 39.54 Significance= 2.5941669E-9 (hom/n)= 0.03 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_201518.1).

25 1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.6.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA36350-1158 (UNQ232))

30 (a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human fibronectin leucine rich transmembrane protein 2 (FLRT2) resulted in greatly reduced viability of (-/-) mutants. Genetic data indicate that this mutation resulted in greatly reduced viability of the homozygous mutants. Three of the identified (-/-) mice were embryonic submissions. The 2 surviving mutant mice were smaller than their wild-type littermates and exhibited numerous abnormalities, including a hearing impairment. Microscopic analysis revealed cardiomyopathy in the homozygous mutants, leading to heart failure. In addition, the female homozygous and heterozygous mice exhibited increased skin fibroblast proliferation rates. In addition, the surviving knockout mice exhibited several immunological abnormalities marked by increased mean serum IgG2a and IgG1 levels. However, a single (-/-) mouse also

exhibited decreased serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge. The surviving (-/-) mice also exhibited decreased total tissue mass, decreased percentage of body fat and decreased fat mass. The female knockout mice showed decreased volumetric bone mineral density (vBMD) and total body mineral bone density (BMD). The male (-/-) mice exhibited increased micro-CT bone measurements. The single female (-/-) mouse also showed a dilated optic disc. Gene disruption was confirmed by Southern blot.

5 (b) Pathology

Microscopic: At 12.5 days, there were 51 embryos observed: 3 (-/-) embryos, 22 (+/-) embryos, 11 (+/+) embryos, 8 resorption moles, and 7 inconclusive. The 3 (-/-) embryos available for analysis exhibited cardiomyopathy, characterized by tightly packed myocytes with highly condensed eosinophilic sarcoplasm. These small dense myocytes were arranged in thin bands that formed the thin walls and trabeculae of the ventricles and atria. The myocytes were surrounded by increased numbers of large primitive endocardial cells that partially filled the ventricular lumen. There was diffuse vascular congestion in the abdominal organs with dilatation of vessels in the embryo, suggesting that congestive heart failure resulted from defective myocardial development. The living (-/-) embryos were generally smaller than their (+/+) littermates, but there was also evidence of embryonic death and resorption at necropsy. The defective structure and arrangement of the cardiac myocytes apparently led to a progressive decrease in prenatal cardiac function, development of heart failure, and embryonic death.

Gene Expression: LacZ activity was detected in the parathyroid among the panel of tissues analyzed by immunohistochemistry.

(c) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 2 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

35 *Prepulse inhibition of the acoustic startle reflex*

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB + 120 dB

- pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

Results:

- 5 Sensorimotor Gating/Attention: Both of the mutant (-/-) mice failed to exhibit a startle response, suggesting hearing impairment in the mutants.

(d) Immunology Phenotypic Analysis

10 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

15 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

20 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic
25 T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

30 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

35 In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and

thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

Serum Immunoglobulin isotyping resulted in the observation that (-/-) mice exhibited an increase in mean serum IgG2a and IgG1 levels compared to the (+/+) littermates, the (+/+) mice within the project run, and the historical means.

Mutant (-/-) mice exhibited elevation of IgG2a and IgG1 serum immunoglobulins compared to their gender-matched (+/+) littermates. These immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. The observed phenotype suggests that the PRO265 polypeptide is a negative regulator of inflammatory responses. These immunological abnormalities suggest that inhibitors (antagonists) of PRO265 polypeptides would be important agents which could stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO265 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

Acute Phase Response:

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sublethal dose of LPS in 200 µL sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 µg/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNFα, MCP-1, and IL-6 on the FACSCalibur instrument.

Results:

The (-/-) mice exhibited decreased mean serum TNF-α, MCP-1 and IL-6 responses to LPS challenge when compared with their (+/+) littermates and the historical means.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO265 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited a decreased ability to elicit an immunological response (TNF-α, MCP-1 and IL-6 production) when challenged with the LPS endotoxin indicating a decreased inflammatory response. TNF-α, MCP-1 and IL-6 contributes to the later stages of B cell activation. In addition, IL-6 plays a critical role in inducing the acute phase response and systemic inflammation.

(e) Phenotypic Analysis: Metabolism -Blood Chemistry

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for

running blood chemistry tests on the mice. In addition to measuring blood glucose levels the following blood chemistry tests are also routinely performed: Alkaline Phosphatase; Alanine Amino-Transferase; Albumin; Bilirubin; Phosphorous; Creatinine; BUN = Blood Urea Nitrogen; Calcium; Uric Acid; Sodium; Potassium; and Chloride. In the area of metabolism, targets may be identified for the treatment of diabetes.

Results:

5 The single male and female (-/-) mice available for analysis exhibited increased uric acid and potassium levels when compared with their gender-matched (+/+) littermate controls and historical means. Thus, mutant (-/-) mice exhibit a negative phenotype associated with notably elevated uric acid in the blood which is indicative of renal calculi (and associated kidney diseases) which is common in a type of gout (abnormal purine metabolism). The heterozygous (+/-) mice also trended higher than the wild-type (+/+) littermate controls.

10 PRO265 polypeptides and agonists thereof would be useful in the treatment of such diseases associated with formation of renal calculi and/or abnormal purine metabolism. In addition, the mutant mice showed decreased mean serum glucose levels which could be associated with the reduced viability of these mice.

(f) *Adult skin cell proliferation:*

Procedure: Skin cells were isolated from 16 week old animals (wild type, heterozygous and 1 homozygous). These were developed into primary fibroblast cultures and the fibroblast proliferation rates were measured in a strictly controlled protocol. The ability of this assay to detect hyper-proliferative and hypo-proliferative phenotypes has been demonstrated with p53 and Ku80. Proliferation was measured using Brdu incorporation.

15

Specifically, in these studies the skin fibroblast proliferation assay was used. An increase in the number of cells in a standardized culture was used as a measure of relative proliferative capacity. Primary fibroblasts were established from skin biopsies taken from wild type and mutant mice. Duplicate or triplicate cultures of 0.05 million cells were plated and allowed to grow for six days. At the end of the culture period, the number of cells present in the culture was determined using a electronic particle counter.

20

Results:

25 One third (1/3) of the heterozygous (+/-) mice exhibited an increased mean skin fibroblast proliferation rate when compared with their gender-matched (+/+) littermates. In addition, the single (-/-) mouse also showed elevated proliferation.

Thus, both homozygous and heterozygous mutant mice demonstrated a hyper-proliferative phenotype. As suggested by these observations, PRO265 polypeptides or agonists thereof could function as tumor suppressors and would be useful in decreasing abnormal cell proliferation.

30

(g) *Bone Metabolism & Body Diagnostics*

(1) Tissue Mass & Lean Body Mass Measurements - DEXA

DEXA Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 1 homozygote were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

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The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software,

the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

5 **Results:**

The single male (-/-) mouse exhibited decreased mean body weight and mean body length (2-3 SD below the mean) when compared with their gender-matched (+/+) littermates and the historical mean.

Fertility:

10 The single male (-/-) mouse available for analysis produced no pups after mating twice with female (+/+) mice thus demonstrating impaired fertility.

(2) **Bone Metabolism: Radiology Phenotypic Analysis**

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- 15 • MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

20 **Procedure:** A cohort of 4 wild type, 4 heterozygotes and 2 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

25 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

30 **Procedure:** MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 2 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

35 **Results:**

DEXA: The single male and single female (-/-) mice available for analysis exhibited decreased total tissue mass, total fat mass, and percent total body fat when compared with their gender-matched (+/+) littermates and the

historical means. In addition, the female knockouts also showed decreased volumetric bone mineral density (vBMD) and total body bone mineral density (BMD).

Micro CT: The single male (-/-) mouse available for analysis (M-225) exhibited increased vertebral trabecular bone volume, number, and connectivity density when compared with its gender-matched (+/+) littermates and the historical means. This is interesting because the mouse is smaller in size.

5 The (-/-) mice analyzed by DEXA and bone micro CT analysis exhibited decreased bone measurements and decreased body mass measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders. In addition, the knockout mice exhibited decreased total tissue mass and body fat suggestive of growth related disorders and/or tissue wasting diseases such as cachexia. These results are consistent with the reduced viability of the (-/-) mice. The (-/-) mice also exhibited a negative bone phenotype with abnormal decreased bone
10 measurements reflective of bone metabolic disorders. The negative bone and metabolic phenotype indicates that PRO265 polypeptides or agonists thereof would be useful for maintaining bone homeostasis or useful for treatment of other metabolic disorders. In addition, PRO265 polypeptides would be useful in bone healing or for the treatment of arthritis or osteoporosis, whereas antagonists (or inhibitors) of PRO265 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with
15 abnormal bone metabolism including arthritis, osteoporosis and osteopenia.

(h) Heart Rate:

Test Description: Heart rate is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. Heart rate is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious heart rate.

20 Results:

The single surviving female (-/-) mouse available for analysis exhibited a notably decreased heart rate (~3 SD below the mean) when compared with its gender-matched (+/+) littermates and the historical mean. These results are consistent with the pathology report indicating a progressive decrease in cardiac function.

25 66.7. Generation and Analysis of Mice Comprising DNA61601-1223 (UNQ272) Gene Disruptions

In these knockout experiments, the gene encoding PRO309 polypeptides (designated as DNA61601-1223) (UNQ272) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_013781 Mus musculus SH2 domain containing 3C (Sh2d3c); protein reference: Q9QZS8 ACCESSION:Q9QZS8 NID: Mus musculus (Mouse). SH2 domain-containing EPH
30 receptor-binding protein SHEP1 (CHAT- H); the human gene sequence reference: BC032365 ACCESSION:BC032365 NID:21619056 Homo sapiens Homo sapiens, SH2 domain-containing 3C, clone MGC:40418 IMAGE:4521962; the human protein sequence corresponds to reference: Q8N5H7 ACCESSION:Q8N5H7 NID: Homo sapiens (Human). SH2 domain-containing 3C.

The mouse gene of interest is Sh2d3c (SH2 domain containing 3C), ortholog of human SH2D3C. Aliases
35 include Chat, Nsp3, Shep1, novel SH2-containing protein 3, Cas/HEF1-associated signal transducer, SH2 domain-containing 3C, and SH2-containing Eph receptor-binding protein 1.

SH2D3C is a cytoplasmic protein that functions as a signal-transducing adaptor molecule, linking small Ras superfamily GTPases to activated receptor-tyrosine kinases. The protein consists of an SH2 domain and a Ras

guanine nucleotide exchange factor domain, suggesting that SH2D3C may also function as a guanine nucleotide exchange factor. SH2D3C binds with GTPases R-Ras and Rap1A, with scaffolding protein Crk-associated substrate (Cas), and with receptor tyrosine kinase EphB2. Moreover, SH2D3C may also function as an adaptor for epidermal growth factor receptor, nerve growth factor receptor, T-cell receptors, and integrins. SH2D3C likely regulates processes such as membrane ruffling, cell migration, T-cell activation, and cytokine production (Dail et al, *J Biol Chem* 279(40):41892-902 (2004); Sakakibara et al, *J Biol Chem* 278(8):6012-7 (2003); Sakakibara et al, *J Cell Sci* 115 (Pt 24):4915-24 (2002); Sakakibara and Hattori, *J Biol Chem* 275(9):6404-10 (2000); Dodelet et al, *J Biol Chem* 274(45):31941-6 (1999)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	44	13	78
Expected	19.5	39.0	19.5	78

Chi-Sq.= 1.66 Significance= 0.43604928 (hom/n)= 0.22 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 4 through 6 were targeted (NCBI accession NM_013781.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.7.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA61601-1223 (UNQ272))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human SH2 domain containing 3C (SH2D3C) resulted in a decreased percentage of CD21^{hi} CD23^{med} B cells in spleen in (-/-) mice. In addition, the (-/-) mice showed decreased mean body weight, decreased mean total tissue mass and lean body mass. Male knockout (-/-) mice exhibited a notably decreased vertebrae bone mineral density (BMD). Gene disruption was confirmed by Southern blot.

(b) Bone Metabolism & Body Diagnostics

(1) Tissue Mass & Lean Body Mass Measurements - DEXA

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position

on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body weight was performed at approximately 16 weeks of age.

5 **Results:**

The male (-/-) mice exhibited decreased mean body weight when compared with their gender-matched (+/+) littermates and the historical mean.

(2) **Bone Metabolism: Radiology Phenotypic Analysis**

10 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

15 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

20 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

25 DEXA: The male (-/-) mice exhibited decreased mean total tissue mass and lean body mass when compared with that of their gender-matched (+/+) littermates and the historical means. In addition, male knockout (-/-) mice showed a notably decreased vertebrae bone mineral density (BMD).

30 The (-/-) mice analyzed by DEXA exhibited notably decreased total tissue mass and lean body mass as well as decreased bone measurements when compared with their (+/+) littermates, suggestive of growth retardation in these mutants. This in conjunction with the observations of decreased body weight suggests a tissue wasting condition such as cachexia or other growth related disorders. Thus, PRO309 polypeptides or agonists thereof would be useful in the treatment or prevention of growth disorders including cachexia or other tissue wasting diseases.

(c) *Immunology Phenotypic Analysis*

35 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly

related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders: Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Flourescence-activated cell-sorting (FACS) Analysis - Tissue Specific FACS

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine

records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

Test Description: The mononuclear cell profile is derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples are analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software

5

Results:

Tissue Specific FACS-Mouse: Analyses of lymphocyte and antigen presenting cell subsets in blood, spleen, bone marrow and peritoneal lavage resulted in the following major findings: Total spleen cell numbers are lower than wildtype or heterozygous littermates. Also observed were statistically significant decreased in knockout cell numbers in the following subsets: spleen - marginal zone B cells, follicular B cells, T1/B cells, T2/marginal zone B cells, activated CD4 T cells, naive CD8 T cells, myeloid dendritic cells and plasmacytoid dendritic cells; bone marrow - total cell numbers, immature B cells, pre-B cells, pro B cells, IgM+ and IgM- plasma cells. The (-/-) mice exhibited a notably decreased percentage of CD21hi CD23med B cells in spleen when compared with that of the (+/+) mice. These results indicate that the knockout mice exhibited a decrease in a subset of B cells (marginal zone B cells) that contain a pool of memory cells and participate in the fast immune response. Thus, the mutant homozygous mice exhibited immunological abnormalities associated with decreased levels of B cell progenitor cells in the spleen.

15

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These results show that knockout (-/-) mice exhibit immunological abnormalities compared to their wild-type (+/+) littermates. Antagonists (inhibitors) of PRO309 polypeptides would be expected to mimic this phenotype. PRO309 polypeptides or agonists thereof would be useful in the development or maturation of B cells which could then participate in fast immune responses.

66.8. Generation and Analysis of Mice Comprising DNA40982-1235 (UNQ293) Gene Disruptions

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In these knockout experiments, the gene encoding PRO332 polypeptides (designated as DNA40982-1235) (UNQ293) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_172874 Mus musculus podocan (Podn); protein reference: Q7TQ62 ACCESSION:Q7TQ62 NID: Mus musculus (Mouse). Podocan protein; the human gene sequence reference: NM_153703 Homo sapiens podocan (PODN); the human protein sequence corresponds to reference: Q5VVZ3 ACCESSION:Q5VVZ3 NID: Homo sapiens (Human). Podocan.

30

The mouse gene of interest is Podn (podocan), ortholog of human PODN. Aliases include Pcan, SLRR5A, 9430070G18, and MGC24995.

35

PODN is a putative secreted protein that can bind with type-1 collagen and likely functions as an extracellular matrix protein. The 611-amino acid protein is a member of the small leucine-rich repeat (SLR) family of non-collagenous extracellular matrix proteins, consisting of a cysteine-rich N terminus, 20 leucine-rich repeats, and an acidic C-terminal domain. Within the renal glomerulus, PODN is expressed in podocytes and vascular endothelial cells and is found in basement membrane. PODN is also expressed in other tissues, including heart and vascular smooth muscle cells. PODN likely modulates fibrillogenesis in glomerular basement membrane and may play a role in glomerular filtration, sclerotic glomerular lesion formation associated with HIV infection, and growth regulation of cardiovascular tissues (Ross et al, J Biol Chem 278(35):33248-55 (2003); Shimizu-Hirota et al, FEBS

Lett 563(1-3):69-74 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd} /C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	24	46	19	89
Expected	22.25	44.5	22.25	89

Chi-Sq.= 2.61 Significance= 0.27117255 (hom/n)= 0.24 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 5 were targeted (NCBI accession NM_172874.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.8.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA40982-1235 (UNQ293)

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human podocan (PODN) resulted in an increased serum IgG3 level. In addition, the mutant (-/-) mice exhibited increased bone mineral density measurements and increased mean femoral mid-shaft cross-sectional area. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate

extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

The (-/-) mice exhibited increased mean serum IgG3 levels compared to their gender-matched (+/+) littermate controls.

The serum immunoglobulin isotyping assay revealed that homozygous adults exhibited increased serum IgG3 levels. Thus, homozygotes showed elevated serum immunoglobulins compared with the (+/+) littermates. IgG3 immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. These immunological abnormalities suggest that antagonists or inhibitors of PRO332 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO332 polypeptides or agonists thereof would inhibit the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(c) *Bone Metabolism & Body Diagnostics: Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

· DEXA for measurement of bone mineral density on femur and vertebra

MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male (-/-) mice exhibited increased mean volumetric bone mineral density and total body bone mineral density when compared with the values for their gender-matched (+/+) littermates and the historical means.

Micro CT: The male (-/-) mice exhibited increased mean femoral mid-shaft cross-sectional area when compared with that of their gender-matched (+/+) littermates and the historical mean.

The male (-/-) mice exhibited increased bone mineral content, and total body and femoral bone mineral density when compared with their gender-matched (+/+) littermates. These results indicate that the knockout mutant phenotype may be associated with such bone abnormalities as osteopetrosis. Osteopetrosis is a condition characterized by abnormal thickening and hardening of bone and abnormal fragility of the bones. As such, PRO332 polypeptides or agonists thereof may be beneficial for the treatment of osteopetrosis. A phenotype associated with an increased bone mineral content, and total body and femoral bone mineral density suggests that agents which mimic these effects (e.g. antagonists of PRO332 polypeptides) would be useful in bone healing.

66.9. Generation and Analysis of Mice Comprising DNA38649 (UNQ301) Gene Disruptions

In these knockout experiments, the gene encoding PRO342 polypeptides (designated as DNA38649) (UNQ301) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_023059 ACCESSION:NM_023059 NID:12746439 Mus musculus Mus musculus single Ig IL-1 receptor related protein (Sigirr-pending); protein reference: Q9JLZ8

ACCESSION:Q9JLZ8 NID: Mus musculus (Mouse). TOLL/INTERLEUKIN-1 RECEPTOR 8; the human gene sequence reference: NM_021805 ACCESSION:NM_021805 NID:11141876 Homo sapiens Homo sapiens single Ig IL-1R-related molecule (SIGIRR); the human protein sequence corresponds to reference: Q9H733 ACCESSION:Q9H733 NID: Homo sapiens (Human). CDNA: FLJ21446 FIS, CLONE COL04458.

5 The mouse gene of interest is AI256711 (expressed sequence AI256711), ortholog of human SIGIRR (single Ig IL-1R-related molecule). Aliases include TIR8, single Ig IL-1R-related protein, and single Ig IL-1 receptor related protein.

SIGIRR is a type I plasma membrane protein that functions as a "non-signaling" or "decoy" receptor. The protein consists of an extracellular immunoglobulin domain, a transmembrane segment, and an intracellular toll/interleukin-1 receptor (TIR) domain. Upon stimulation, proinflammatory interleukin-1 receptor (IL-1R) and toll-like receptors (TLRs) recruit SIGIRR, which then sequesters downstream signaling molecules interleukin-1 receptor-associated kinase (IRAK) and TNF receptor-associated factor 6 (TRAF6), inhibiting signal transduction. SIGIRR is involved in negatively modulating innate immune responses. The protein is expressed in many tissues and cells, including dendritic cells and epithelial cells in kidney, colon, and other mucosal tissues, and is down-regulated in response to lipopolysaccharides (LPS). Thus, SIGIRR blocks innate immune reactions in non-stimulated cells, presumably preventing detrimental effects, such as chronic inflammation and sepsis (Thomassen et al, *Cytokine* 11(6):389-99 (1999); Polentarutti et al, *Eur Cytokine Netw* 14(4):211-8 (2003); Wald et al, *Nat Immunol* 4(9):920-7 (2003); Mantovani et al, *J Leukoc Biol* 75(5):738-42 (2004); O'Neill, *Nat Immunol* 4(9):823-4 (2003); Garlanda et al, *Proc Natl Acad Sci U S A* 101(10):3522-6 (2004)).

20 Wald and colleagues [*Nat Immunol* 4(9):920-7(2003)], as well as Garlanda and colleagues [*Proc Natl Acad Sci U S A* 101(10):3522-6(2004)], investigated the physiological role of SIGIRR using knockout mice. They showed that inflammation in response to IL-1 or LPS and intestinal inflammation susceptibility was greater in SIGIRR-deficient mice than in wild-type mice. These authors concluded that SIGIRR is essential for modulating innate immune responses and may be important for regulating inflammation in the gastrointestinal tract.

25 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	18	20	54
Expected	13.5	27	13.5	54

Chi-Sq.= 0.73 Significance= 0.69419664 (hom/n)= 0.26 Avg. Litter Size= 8

Mutation Information

35 Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 9 were targeted (NCBI accession NM_023059.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.9.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA38649 (UNO301))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human single Ig IL-1R-related molecule (SIGIRR) resulted in a decreased mean percentage of CD4 cells in the peripheral blood as well as a decreased mean serum IgA level. The homozygous mice also showed a decreased pain response (decreased sensitivity to heat-induced pain). In addition, the mutant male (-/-) and (+/-) mice showed increased mean serum cholesterol and triglyceride levels. Radiology results indicated that the female (-/-) mice showed decreased bone mineral content and bone mineral density index measurements. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides.

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes.

Blood Lipids

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The male (-/-) and (+/-) mice exhibited increased mean serum cholesterol and triglyceride levels [cholesterol > 2 SD in (-/-) males; > 2 SD in (+/-) males; triglycerides > 1-2 SD in (-/-) males] when compared with their gender-matched (+/+) littermates and the historical means.

As summarized above, the (-/-) mice exhibited notably increased mean serum cholesterol and triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO342 gene can serve as a model for cardiovascular disease. PRO342 polypeptides or its encoding gene would be useful in regulating blood lipids such as cholesterol and triglycerides. Thus, PRO342 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, hypertriglyceridemia, diabetes and/or obesity.

(c) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often

multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

5 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

10 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also
15 secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

 In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

20 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

25 In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and
30 thus ameliorate immune related disease.

 The following test was performed:

 (1) *Flourescence-activated cell-sorting (FACS) Analysis*

 Procedure:

35 FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

 In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and

lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

5 The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

10 FACS3: The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by a decreased mean percentage of CD4 cells when compared with their (+/+) littermates, the (+/+) mice for the project run and the historical mean.

The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by decreased mean percentages of CD4 cells in the cell population when compared with their (+/+) littermates and the historical means.

15 Thus, knocking out the gene which encodes PRO342 polypeptides causes a decrease in the T cell population. From these observations, PRO342 polypeptides or the gene encoding PRO342 appears to act as a regulator of T cell proliferation. Thus, PRO342 polypeptides would be beneficial in enhancing T cell proliferation.

(2) *Serum Immunoglobulin Isotyping Assay:*

20 The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

25 The (-/-) mice exhibited a decreased mean serum IgA level when compared with that of their (+/+) littermates, the (+/+) mice for the project run, and the historical median.

30 These results suggest that the phenotype associated with these knockout mice is immunoglobulin deficiency in IgA. The most common inherited form of immunoglobulin deficiency is selective IgA deficiency, which is seen in about one person in 800. IgA mainly functions as an epithelial cell protector which can neutralize bacterial toxins and viruses. Although no obvious disease susceptibility is associated with selective IgA defects, they are commoner in people with chronic lung disease than in the general population. This suggests that lack of IgA may result in a predisposition to lung infections with various pathogens and is consistent with the role of IgA in defense at the body surfaces. Thus PRO342 polypeptides or agonists thereof, play an important role in protecting against as a natural immunity protection against skin infections and more importantly would prevent susceptibility to lung infections.

35 (d) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory

disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Hot Plate Testing

Test Description: The hot plate test for nociception is carried out by placing each mouse on a small enclosed 55° C hot plate. Latency to a hindlimb response (lick, shake, or jump) is recorded, with a maximum time on the hot plate of 30 sec. Each animal is tested once.

Results:

Hot Plate: The (-/-) mice exhibited an increased latency to respond during hot plate testing when compared with their (+/+) littermates and the historical mean, suggesting decreased sensitivity to acute pain in the mutants.

(e) *Bone Metabolism & Body Diagnostics: Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5

vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The female (-/-) mice exhibited decreased mean bone mineral content, bone mineral density index, and bone mineral density in total body, femurs, and vertebrae when compared with their gender-matched (+/+) littermates and the historical means.

The (-/-) mice analyzed by DEXA and bone micro CT analysis exhibited decreased bone measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders. The (-/-) mice exhibited a negative bone phenotype with abnormal decreased bone measurements reflective of bone metabolic disorders. The negative bone phenotype indicates that PRO342polypeptides or agonists thereof would be useful for maintaining bone homeostasis. In addition, PRO342polypeptides would be useful in bone healing or for the treatment of arthritis or osteoporosis, whereas antagonists (or inhibitors) of PRO342polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with abnormal bone metabolism including arthritis, osteoporosis and osteopenia.

66.10. Generation and Analysis of Mice Comprising DNA47470-1130P1 (UNQ313) Gene Disruptions

In these knockout experiments, the gene encoding PRO356 polypeptides (designated as DNA47470-1130P1) (UNQ313) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: BC023373 ACCESSION:BC023373 NID:19483941 Mus musculus Mus musculus, Similar to angiotensin-like factor, clone MGC:32448 IMAGE:5043159; protein reference: Q8R1Q3 ACCESSION:Q8R1Q3 NID: Mus musculus (Mouse). Similar to angiotensin-like factor (Mus musculus 13 days embryo male testis cDNA, RIKEN full-length enriched library, clone:6030482D04 product:CDT6 (ANGIOTENSIN-LIKE FACTOR) (CDT6 PROTEIN) homolog); the human gene sequence reference: NM_021146 ACCESSION:NM_021146 NID:20127595 Homo sapiens Homo sapiens angiotensin-like factor (CDT6); the human protein sequence corresponds to reference: O43827 ACCESSION:O43827 NID: Homo sapiens (Human). CDT6 (ANGIOTENSIN-LIKE FACTOR) (CDT6 PROTEIN).

The mouse gene of interest is defined as "similar to angiotensin-like factor," which is the ortholog of human CDT6 (cornea-derived transcript 6). Aliases include angiotensin-like factor, AngX, and dJ647M16.1.

CDT6 is a secreted protein expressed in corneal stroma that likely functions as a ligand. CDT6 is structurally similar to proteins of the angiotensin family, which bind to receptors that generally regulate angiogenesis. In a mouse xenograft model, CDT6 inhibited tumor growth and aberrant blood vessel formation and stimulated extracellular matrix deposition. Thus, CDT6 likely prevents vascularization in the cornea and functions as a morphogen that induces a corneal phenotype. The potential of CDT6 as an anti-tumor agent, however, is questionable (Peek et al, *Invest Ophthalmol Vis Sci* 39(10):1782-8 (1998); Peek et al, *J Biol Chem* 277(1):686-93 (2002); Bouis et al, *In Vivo* 17(2):157-61 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	19	45	14	78
Expected	19.5	39	19.5	78

Mutation Information

10 Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession BC023373).

Chi-Sq.= 0.21 Significance= 0.9003245 (hom/n)= 0.26 Avg. Litter Size= 9

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except heart.

15 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.10.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA47470-1130P1 (UNQ313))

(a) *OVERALL PHENOTYPIC SUMMARY:*

20 Mutation of the gene encoding the ortholog of human cornea-derived transcript 6 (CDT6) resulted in increased bone mineral density measurements in the (-/-) mice. Gene disruption was confirmed by Southern blot.

(b) *Bone Metabolism & Body Diagnostics: Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- 25 · MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

30 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImusTM Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, 35 the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1

femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male (-/-) mice exhibited increased mean volumetric bone mineral density in total body and femur when compared with their gender-matched (+/+) littermates and the historical means.

Micro CT: The male (-/-) mice exhibited increased mean femoral mid-shaft cross-sectional area when compared with their gender-matched (+/+) littermates and the historical mean.

The male (-/-) mice exhibited increased bone mineral content, and total body and femoral mid-shaft cross-sectional area when compared with their gender-matched (+/+) littermates. These results indicate that the knockout mutant phenotype may be associated with such bone abnormalities as osteopetrosis. Osteopetrosis is a condition characterized by abnormal thickening and hardening of bone and abnormal fragility of the bones. As such, PRO356 polypeptides or agonists thereof would be beneficial for the treatment of osteopetrosis. A phenotype associated with an increased bone mineral content, and total body and femoral bone mineral density suggests that agents which mimic these effects (e.g. antagonists of PRO356 polypeptides) would be useful in bone healing.

66.11. Generation and Analysis of Mice Comprising DNA44189-1322 (UNQ341) Gene Disruptions

In these knockout experiments, the gene encoding PRO540 polypeptides (designated as DNA44189-1322) (UNQ341) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_133792 Mus musculus lysophospholipase 3 (Lypla3); protein reference: Q8VEB4 ACCESSION:Q8VEB4 NID: Mus musculus (Mouse). Similar to LCAT-like lysophospholipase (Lysosomal phospholipase A2); the human gene sequence reference: NM_012320 ACCESSION:NM_012320 NID: gi 20302150 ref NM_012320.2 Homo sapiens lysophospholipase 3 (lysosomal phospholipase A2) (LYPLA3); the human protein sequence corresponds to reference: Q8NCC3 ACCESSION:Q8NCC3 NID: Homo sapiens (Human). Hypothetical protein FLJ90347.

The mouse gene of interest is Lypla3 (lysophospholipase 3), ortholog of human LYPLA3 (lysophospholipase 3 [lysosomal phospholipase A2]). Aliases include ACS, LLPL, LPLA2, lysosomal phospholipase A2, DKFZp564A0122, 1-O-acylceramide synthase, and LCAT-like lysophospholipase.

LYPLA3 is a likely lysosomal enzyme that functions as an acyltransferase, catalyzing the transfer of acyl groups at the sn-2 position in phospholipids to the C-1 hydroxyl group of ceramide, forming 1-O-acylceramide. In the absence of ceramide, the enzyme can also function as a phospholipase, forming lysophospholipid and free fatty acid from phospholipids. The enzyme may also have weak lysophospholipase activity and has been detected in plasma. LYPLA3 is calcium-independent, is optimally active at acidic pH, and is expressed in a wide variety of tissues (Taniyama et al, Biochem Biophys Res Commun 257(1):50-6 (1999); Hiraoka et al, J Biol Chem 277(12):10090-9 (2002)). LYPLA3 may play a role in lung surfactant catabolism by alveolar macrophages (Abe

et al, *J Biol Chem* 279(41):42605-11 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	23	33	19	75
Expected	18.75	37.5	18.75	75

Chi-Sq.= 1.53 Significance= 0.46533394 (hom/n)= 0.26 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_133792.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.11.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA44189-1322 (UNQ341))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human lysophospholipase 3 (lysosomal phospholipase A2) (LYPLA3) resulted in decreased bone mineral density measurements in the male (-/-) mice. The knockout mice also exhibited an impaired glucose tolerance. Gene disruption was confirmed by Southern blot.

(b) *Bone Metabolism & Body Diagnostics: Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImusTM Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male (-/-) mice exhibited decreased mean bone mineral content and bone mineral density in total body femur and vertebrae when compared with the values for their gender-matched (+/+) littermates and the historical means. However, difference in vertebrae bone mineral density is ~ 1-SD below the median.

Micro CT: The male (-/-) mice exhibited decreased mean femoral mid-shaft cross-sectional area when compared with that of their gender-matched (+/+) littermates and the historical mean.

The (-/-) mice analyzed by DEXA and bone micro CT analysis exhibited decreased bone measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders. The (-/-) mice exhibited a negative bone phenotype with abnormal decreased bone measurements reflective of bone metabolic disorders. The negative bone phenotype indicates that PRO540 polypeptides or agonists thereof would be useful for maintaining bone homeostasis. In addition, PRO540 polypeptides would be useful in bone healing or for the treatment of arthritis or osteoporosis, whereas antagonists (or inhibitors) of PRO540 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with abnormal bone metabolism including arthritis, osteoporosis and osteopenia.

(c) Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygote mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:Blood Glucose Levels/Glucose Tolerance Test:

The male (-/-) mice exhibited impaired glucose tolerance when placed on a high fat diet compared with their gender-matched (+/+) littermates and the historical means.

These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose homeostasis, and therefore PRO540 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

66.12. Generation and Analysis of Mice Comprising DNA49152-1324 (UNQ354) Gene Disruptions

In these knockout experiments, the gene encoding PRO618 polypeptides (designated as DNA49152-1324) (UNQ354) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: BC029645 ACCESSION:BC029645 NID:20987285 Mus musculus Mus musculus transmembrane serine protease 6, mRNA (cDNA clone MGC:25857 IMAGE:4195486); protein reference: Q9DBI0 ACCESSION:Q9DBI0 NID: Mus musculus (Mouse). 1300008A22RIK PROTEIN; the human gene sequence reference: NM_153609 Homo sapiens transmembrane protease, serine 6 (TMPRSS6); the human protein sequence corresponds to reference: Q8IU80 ACCESSION:Q8IU80 NID: Homo sapiens (Human). Type II transmembrane serine protease 6.

The mouse gene of interest is Tmprss6 (transmembrane serine protease 6), ortholog of human TMPRSS6. Aliases include 1300008A22Rik, matriptase-2, type II transmembrane serine protease 6, FLJ30744, and membrane-bound mosaic serine proteinase.

TMPRSS6 is a type II plasma membrane protein expressed primarily in liver that functions as a trypsin-like serine protease, catalyzing the hydrolysis of extracellular matrix proteins. TMPRSS6 likely plays a role in extracellular matrix remodeling in liver. TMPRSS6 is elevated in invasive ductal cell carcinoma, suggesting that TMPRSS6 may also play a role in metastasis (Hooper et al, *Biochem J* 373(Pt 3):689-702 (2003); Overall et al, *Biol Chem* 385(6):493-504 (2004); Velasco et al, *J Biol Chem* 277(40):37637-46 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	26	41	14	81
Expected	20.25	40.5	20.25	81

Chi-Sq.= 2.05 Significance= 0.35879648 (hom/n)= 0.21 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 3 were targeted (NCBI accession NM_027902.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except thymus, spleen, lung, skeletal muscle, bone, and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.12.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA49152-1324 (UNQ354))

(a) *OVERALL PHENOTYPIC SUMMARY:*

5 Mutation of the gene encoding the ortholog of human transmembrane serine protease 6 (TMPRSS6) resulted in the homozygous mutant mice exhibiting signs of growth retardation, including decreased body weight and length, total tissue mass, and lean body mass and decreased bone mineral content and density measurements. The mutant (-/-) mice also showed signs of anemia and an increased mean platelet count. Circadian testing revealed no circadian rhythm (or hypoactivity). In addition, the mutants exhibited alopecia, hypochromasia and anisocytosis characterized by abnormal erythrocytes suggestive of a defect in RBCs or hemoglobin. Gene
10 disruption was confirmed by Southern blot.

(b) *Pathology*

Gross Observations: The (-/-) mice exhibited alopecia and epidermal hyperkeratosis.

Microscopic: The (-/-) mice exhibited hypochromasia and anisocytosis, characterized by abnormal erythrocytes that contained less than normal amount of hemoglobin and by less than expected levels of erythropoiesis in the
15 bone marrow and spleen, suggestive of a defect in red blood cell or hemoglobin production. In addition, the (-/-) mutants exhibited diffuse alopecia and epidermal hyperkeratosis.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Immunology Phenotypic Analysis*

20 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

25 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

30 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also
35 secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination

of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Hematology Analysis:

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

Results:

Hematology: The (-/-) mice exhibited decreased mean hemoglobin and hematocrit levels and an increased mean red blood cell count when compared with the levels in their (+/+) littermates and the historical means. In addition, the mean corpuscular volume and mean corpuscular hemoglobin were decreased in the (-/-) mice whereas the red cell distribution width was increased, indicating that the size of the red blood cells was variable in the mutants. The (-/-) mice also exhibited an increased mean platelet count.

These results are related to a phenotype associated with anemia. Thus, PRO618 polypeptides, agonists thereof or the encoding gene for PRO618 polypeptides must be essential for normal red blood cell production and as such would be useful in the treatment of blood disorders associated with anemia or a low hematocrit.

In addition, the (-/-) mice exhibited an increased mean platelet count when compared with their (+/+) littermates and the historical mean. Thus, mutant mice deficient in the DNA49152-1324 gene resulted in a phenotype related to coagulation disorders.

(d) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood

disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

(1) *Circadian Test Description:*

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The female (-/-) mice exhibited hypoactivity with no circadian rhythm and hypoactivity during the 1-hour and 12-hour habituation periods and all light and dark periods suggesting an abnormal sleep/wake cycle during the last 24 hours of testing when compared with the levels measured in their gender-matched (+/+) littermates and the historical means. These results demonstrate an abnormal circadian rhythm. Home-cage activity testing is also suggestive of decreased activity or hypoactivity which is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO618 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

(2) *Functional Observational Battery (FOB) Test*

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Results:

All 8 of the (-/-) mice exhibited thinning fur and/or bald patches.

(e) *Bone Metabolism & Body Diagnostics*

(1) *Tissue Mass & Lean Body Mass Measurements - DEXA*

DEXA Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20

ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

5 Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

The male (-/-) mice exhibited decreased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean.

10 Obvious General Appearance: The (-/-) mice exhibited alopecia in the dorsal and ventral regions of the thorax and abdomen. The tails of all of the (-/-) mice and some of the (+/-) mice appeared shorter with lateral curvature or slight kinks.

(2) Bone Metabolism: Radiology Phenotypic Analysis

15 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

• DEXA for measurement of bone mineral density on femur and vertebra

Dexa Analysis - Test Description:

20 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

25 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

30 DEXA: Both the male and female (-/-) mice exhibited decreased lean body mass, and bone mineral content and density measurements when compared with those of their gender-matched (+/+) littermates and the historical means. Male knockouts also showed decreased mean total tissue mass (TTM).

35 Mutant (-/-) mice deficient in the gene encoding PRO618 polypeptides show a phenotype consistent with growth retardation and tissue wasting diseases marked by decreased mean total mass, lean body mass. These results are consistent with the observation of decreased mean body weight and mean body length reported above. In addition, the mutant (-/-) mice exhibited decreased bone mineral content and density measurements suggestive of osteoporosis. Thus, antagonists or inhibitors of PRO618 polypeptides or its encoding gene would mimic these abnormal metabolic related effects. On the other hand, PRO618 polypeptides or agonists thereof would be useful in the prevention and/or treatment of such metabolic disorders related to growth or diseases such as cachexia or other tissue wasting diseases as well as useful in the treatment of bone disorders associated with bone loss.

66.13. Generation and Analysis of Mice Comprising DNA52185-1370 (UNQ481) Gene Disruptions

In these knockout experiments, the gene encoding PRO944 polypeptides (designated as DNA52185-1370) (UNQ481) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_016674 Mus musculus claudin 1 (Cldn1); protein reference: O88551 ACCESSION:O88551 NID: Mus musculus (Mouse). Claudin-1; the human gene sequence reference: NM_021101 ACCESSION:NM_021101 NID: gi21536297 refNM_021101.3 Homo sapiens claudin 1 (CLDN1); the human protein sequence corresponds to reference: O95832 ACCESSION:O95832 NID: Homo sapiens (Human). Claudin-1 (Senescence-associated epithelial membrane protein).

The mouse gene of interest is Cldn1 (claudin 1), ortholog of human CLDN1. Aliases include CLD1, SEMP1, and senescence-associated epithelial membrane protein 1.

CLDN1 is an integral plasma membrane protein that functions as a component of tight junctions, cell adhesion molecules that form a barrier between cells to limit paracellular transport of solutes and water. The extracellular segments of CLDN1 interact adhesively with claudins on adjacent cells and co-polymerize laterally, forming tight junction strands. CLDN1 is expressed in liver, airway epithelium, pancreas, placenta, adrenals, prostate and ovary. CLDN1 likely plays an important role in maintenance and regulation of cell polarity and permeability (Furuse et al, *J Cell Biol* 141(7):1539-50 (1998); Swisshelm et al, *Gene* 226(2):285-95 (1999); Heiskala et al, *Traffic* 2(2):93-8 (2001); Furuse et al, *J Cell Biol* 156(6):1099-111 (2002); Coyne et al, *Am J Physiol Lung Cell Mol Physiol* 285(5):L1166-78 (2003); Sasaki et al, *Proc Natl Acad Sci U S A* 100(7):3971-6 (2003)).

Furuse and colleagues (2002) investigated the physiological role of CLDN1 using knockout mice. CLDN1 homozygous null mice died within 1 day after birth. Although tight junctions were clearly evident in the epidermis of CLDN1 homozygous null mice, 600-dalton tracer dye diffused through epidermal tight junctions of the CLDN1 homozygous null mice but not through those of the wild-type mice. Furuse and colleagues concluded that CLDN1 is required for barrier function in mammalian skin.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	40	2	60
Expected	15.0	30	15.0	60

Chi-Sq.= 12.72 Significance= 0.0017293665 (hom/n)= 0.12 Avg. Litter Size= 9

Mutation Type: Homologous Recombination (standard)

Coding exon 1 was targeted (NCBI accession NM_016674.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone, heart, and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.13.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA52185-1370 (UNQ481))(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human claudin 1 (CLDN1) resulted in lethality of (-/-) mutants. The (-/-) pups were dead at the time of genotyping. Gene disruption was confirmed by Southern blot.

(b) *Pathology*

5 Microscopic: At 12.5 days, there were 41 embryos observed: 9 (-/-) embryos, 20 (+/-) embryos, 8 (+/+) embryos, 2 resorption moles, 1 to-be-determined, and 1 inconclusive. No developmental abnormalities were detected in the 12.5 day mutant embryos by histologic examination.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

Discussion related to embryonic developmental abnormality of lethality:

10 Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethal mice are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative
15 clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

66.14. Generation and Analysis of Mice Comprising DNA58855-1422 (UNQ518) Gene Disruptions

20 In these knockout experiments, the gene encoding PRO994 polypeptides (designated as DNA58855-1422) (UNQ518) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_025453 ACCESSION:NM_025453 NID: gi 13384857 ref NM_025453.1 Mus musculus RIKEN cDNA 1810018L02 gene (1810018L02Rik); protein reference: Q9CQY8 ACCESSION:Q9CQY8 NID: Mus musculus (Mouse). 1810018L02Rik protein; the human gene sequence reference: NM_024795 ACCESSION:NM_024795 NID: gi 13376165 ref NM_024795.1 Homo sapiens
25 hypothetical protein FLJ22800 (FLJ22800); the human protein sequence corresponds to reference: Q9H5X9 ACCESSION:Q9H5X9 NID: Homo sapiens (Human). Hypothetical protein FLJ22800.

The mouse gene of interest is RIKEN cDNA 1810018L02 gene, ortholog of human hypothetical protein FLJ22800.

30 Hypothetical protein FLJ22800 is a putative integral plasma membrane protein, consisting of a signal peptide and four transmembrane domains contained within an L6 membrane protein domain (Pfam accession PF05805). The function of this hypothetical protein is unknown; however, other L6 membrane family members have been implicated in cancer (Wright et al, *Protein Sci* 9(8):1594-600 (2000)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are
35 intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	41	23	80
Expected	20	40	20	80

Chi-Sq.= 1.62 Significance= 0.44485807 (hom/n)= 0.25 Avg. Litter Size= 9

Mutation Information

5 Mutation Type: Homologous Recombination (standard).

Description: Coding exon 1 was targeted (NCBI accession NM_025453.1).

1. Wild-type Expression Panel: Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

10

66.14.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA58855-1422 (UNQ518))

(a) *OVERALL PHENOTYPIC SUMMARY:*

15 Mutation of the gene encoding the ortholog of a human hypothetical protein (FLJ22800) resulted in a decreased anxiety-related response in (-/-) mice. UNQ518 is expressed at higher levels in the pancreas and small intestine compared with other tissues. The (-/-) mice also exhibited enhanced motor coordination. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: CNS/Neurology*

20 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

30

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Open field test:

35

Several targets of known drugs have exhibited phenotypes in the open field test. These include knockouts of the serotonin transporter, the dopamine transporter (Giros et al., Nature. 1996 Feb 15;379(6566):606-12), and the GABA receptor (Homanics et al., Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):4143-8). An automated open-field assay was customized to address changes related to affective state and exploratory patterns related to

learning. First, the field (40 X 40 cm) was selected to be relatively large for a mouse, thus designed to pick up changes in locomotor activity associated with exploration. In addition, there were 4 holes in the floor to allow for nose-poking, an activity specifically related to exploration. Several factors were also designed to heighten the affective state associated with this test. The open-field test is the first experimental procedure in which the mice are tested, and the measurements that were taken were the subjects' first experience with the chamber. In addition, the open-field was brightly lit. All these factors will heighten the natural anxiety associated with novel and open spaces. The pattern and extent of exploratory activity, and especially the center-to-total distance traveled ratio, may then be able to discern changes related to susceptibility to anxiety or depression. A large arena (40 cm x 40 cm, VersaMax animal activity monitoring system from AccuScan Instruments) with infrared beams at three different levels was used to record rearing, hole poke, and locomotor activity. The animal was placed in the center and its activity was measured for 20 minutes. Data from this test was analyzed in five, 4-minute intervals. The total distance traveled (cm), vertical movement number (rearing), number of hole pokes, and the center to total distance ratio were recorded.

The propensity for mice to exhibit normal habituation responses to a novel environment is assessed by determining the overall change in their horizontal locomotor activity across the 5 time intervals. This calculated slope of the change in activity over time is determined using normalized, rather than absolute, total distance traveled. The slope is determined from the regression line through the normalized activity at each of the 5 time intervals. Normal habituation is represented by a negative slope value.

Results:

The (-/-) mice exhibited an increased median sum time-in-center during open field testing when compared with their gender-matched (+/+) littermates and the historical mean, suggesting a decreased anxiety-like response in the mutants.

A notable difference was observed during open field activity testing. The male (-/-) mice exhibited an increased median sum time in the center area when compared with their gender-matched (+/+) littermates, which is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO994 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

Circadian Test Description:

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The female (-/-) mice exhibited decreased ambulatory activity during the 12-hour habituation period and all light and dark periods suggesting an abnormal sleep/wake cycle during the last 24 hours of testing when

compared with the levels measured in their gender-matched (+/+) littermates and the historical means. These results demonstrate an abnormal circadian rhythm. Home-cage activity testing is also suggestive of decreased activity or hypoactivity which is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO994 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

Inverted Screen Testing:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Inverted Screen Test Data:

The Inverted Screen is used to measure motor strength/coordination. Untrained mice were placed individually on top of a square (7.5 cm x 7.5 cm) wire screen which was mounted horizontally on a metal rod. The rod was then rotated 180 degrees so that the mice were on the bottom of the screens. The following behavioral responses were recorded over a 1 min testing session: fell off, did not climb, and climbed up.

Results:

Genotype	Ratio Fell Down %		Ratio Climbed up %	
+/+ (n=8)	0/8	0	4/8	50
-/- (n=8)	0/8	0	8/8	100
wt population	Fell Down 3.62%		Climbed up 60.04%	

A motor strength deficit is apparent when there is a 50% point difference between (-/-) or (+/-) mice and (+/+) mice for the fell down response. 0/8 or 1/8 (-/-) or (+/-) mice not climbing indicates impaired motor coordination. 7/8 or 8/8 (-/-) or (+/-) mice climbing up indicates enhanced motor coordination.

The Inverted Screen Test is designed to measure basic sensory & motor observations:

Among the 8 (-/-) mice analyzed, all 8 (-/-) mice climbed up the screen whereas 4/8 (+/+) mice climbed up, suggesting an enhanced motor coordination in the mutants.

66.15. Generation and Analysis of Mice Comprising DNA56050-1455 (UNQ536) Gene Disruptions

In these knockout experiments, the gene encoding PRO1079 polypeptides (designated as DNA56050-1455) (UNQ536) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_029537 ACCESSION:NM_029537 NID: gi 22095006 ref NM_029537.1 Mus musculus RIKEN cDNA 6530411B15 gene (6530411B15Rik); protein reference: Q91X86 ACCESSION:Q91X86 NID: Mus musculus (Mouse). Unknown (Protein for MGC:19304); the human gene sequence reference: NM_015544 ACCESSION:NM_015544 NID: gi 7661615 ref NM_015544.1 Homo sapiens DKFZP564K1964 protein (DKFZP564K1964); the human protein sequence corresponds to reference: Q9Y2Y6 ACCESSION:Q9Y2Y6 NID: Homo sapiens (Human). TADA1 protein (DKFZP564K1964 protein).

The mouse gene of interest is RIKEN cDNA 6530411B15 gene, ortholog of human DKFZP564K1964 protein. Aliases include TADA1 protein, ETVV536, and UNQ536.

DKFZP564K1964 protein is a putative secreted protein, consisting of a weakly predicted signal peptide

and no other conserved domain.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	11	31	2	44
Expected	11	22	11	44

Chi-Sq= 13.06 Significance= 0.0014590055 (hom/n)= 0.09 Avg. Litter Size= 7

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_029537.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

Reduced viability of (-/-) mice was observed. Seven of the (-/-) mice identified were submitted as embryonic samples.

66.15.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA56050-1455 (UNQ536))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of a human putative secreted protein resulted in greatly reduced viability of (-/-) mutants. Seven of the (-/-) mice identified were submitted as embryonic samples.

Of the 2 surviving mutants, the male died shortly after blood pressure analysis, while the female underwent the majority of Level 1 testing. The homozygous mutants exhibited numerous immunological abnormalities including anemia. Open field testing results indicated hyperactivity in the mutant (-/-) mice. The single male (-/-) mouse exhibited decreased total tissue mass and lean body mass but the female (-/-) knockout showed increased total tissue mass, fat mass (g) and % total body fat. One mouse exhibited retinal hemorrhage. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

Microscopic: At day 12.5, there were 39 embryos observed: 7 (-/-) embryos, 9 (+/-) embryos, 9 (+/+) embryos, 4 resorption moles, and 10 inconclusive. The (-/-) embryos were generally smaller than their (+/+) littermates but no other developmental abnormalities were detected in the day 12.5 embryos.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory

disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 2 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Open field test:

Several targets of known drugs have exhibited phenotypes in the open field test. These include knockouts of the serotonin transporter, the dopamine transporter (Giros et al., Nature. 1996 Feb 15;379(6566):606-12), and the GABA receptor (Homanics et al., Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):4143-8). An automated open-field assay was customized to address changes related to affective state and exploratory patterns related to learning. First, the field (40 X 40 cm) was selected to be relatively large for a mouse, thus designed to pick up changes in locomotor activity associated with exploration. In addition, there were 4 holes in the floor to allow for nose-poking, an activity specifically related to exploration. Several factors were also designed to heighten the affective state associated with this test. The open-field test is the first experimental procedure in which the mice are tested, and the measurements that were taken were the subjects' first experience with the chamber. In addition, the open-field was brightly lit. All these factors will heighten the natural anxiety associated with novel and open spaces. The pattern and extent of exploratory activity, and especially the center-to-total distance traveled ratio, may then be able to discern changes related to susceptibility to anxiety or depression. A large arena (40 cm x 40 cm, VersaMax animal activity monitoring system from AccuScan Instruments) with infrared beams at three different levels was used to record rearing, hole poke, and locomotor activity. The animal was placed in the center and its activity was measured for 20 minutes. Data from this test was analyzed in five, 4-minute intervals. The total distance traveled (cm), vertical movement number (rearing), number of hole pokes, and the center to total distance ratio were recorded.

The propensity for mice to exhibit normal habituation responses to a novel environment is assessed by determining the overall change in their horizontal locomotor activity across the 5 time intervals. This calculated slope of the change in activity over time is determined using normalized, rather than absolute, total distance traveled. The slope is determined from the regression line through the normalized activity at each of the 5 time intervals. Normal habituation is represented by a negative slope value.

Results:

Anxiety: The (-/-) mice exhibited increased sum total distance traveled during open field testing when compared with their gender-matched (+/+) littermates and the historical mean, suggesting hyperactivity or an increased

anxiety-like response in the mutants.

In summary, the open field testing revealed a phenotype associated with increased anxiety which could be associated with mild to moderate anxiety, anxiety due to a general medical condition, and/or bipolar disorders; hyperactivity; sensory disorders; obsessive-compulsive disorders, schizophrenia or a paranoid personality. Thus, PRO1079 polypeptides or agonists thereof would be useful in the treatment of such neurological disorders.

5

(d) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

(1) *Hematology Analysis:*

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

Results:

5 Hematology: The female (-/-) mouse available for analysis was anemic, exhibiting a decreased red blood cell count, hemoglobin concentration, and hematocrit with an increase in mean corpuscular volume and red blood cell distribution width when compared with their (+/+) littermates and the historical means.

These results are related to a phenotype associated with anemia. Thus, PRO1079 polypeptides, agonists thereof or the encoding gene for PRO1079 polypeptides must be essential for normal red blood cell production and as such would be useful in the treatment of blood disorders associated with anemia or a low hematocrit.

(2) *Flourescence-activated cell-sorting (FACS) Analysis*

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 1 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

FACS3: The single female (-/-) mouse analyzed exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by an increased percentage of natural killer cells when compared with its (+/+) littermates and the historical mean.

30 FACS results indicate that the homozygous mutant mice have an increased mean percentage of natural killer cells. Thus, PRO1079 polypeptides or agonists thereof function as negative regulators of NK cell production. Natural killer cells are the first line of defense to viral infection since these cells have been implicated in viral immunity and in defense against tumors. Natural killer cells or NK cells act as effectors in antibody-dependent cell-mediated cytotoxicity and have been identified by their ability to kill certain lymphoid tumor cell lines *in vitro* without the need for prior immunization or activation. Thus, antagonists (inhibitors) of PRO1079 polypeptides would be useful in the production of NK cells which are important for antibody dependent cell-mediated cytotoxicity.

(3) *Ovalbumin Challenge*

Procedure: This assay was carried out on 7 wild types and 2 homozygotes. Chicken ovalbumin (OVA) is a T-cell dependent antigen, which is commonly used as a model protein for studying antigen-specific immune responses in mice. OVA is non-toxic and inert and therefore will not cause harm to the animals even if no immune response is induced. The murine immune response to OVA has been well characterized, to the extent that the immunodominant peptides for eliciting T cell responses have been identified. Anti-OVA antibodies are detectable 8 to 10 days after immunization using enzyme-linked immunosorbent assay (ELISA), and determination of different isotypes of antibodies gives further information on the complex processes that may lead to a deficient response in genetically engineered mice.

As noted above, this protocol assesses the ability of mice to raise an antigen-specific immune response. Animals were injected IP with 50 mg of chicken ovalbumin emulsified in Complete Freund's Adjuvant and 14 days later the serum titer of anti-ovalbumin antibodies (IgM, IgG1 and IgG2 subclasses) was measured. The amount of OVA-specific antibody in the serum sample is proportional to the Optical Density (OD) value generated by an instrument that scans a 96-well sample plate. Data was collected for a set of serial dilutions of each serum sample.

Results of this challenge:

The (-/-) mice exhibited decreased (low/no) mean serum IgG1 and IgG2a responses when compared with their (+/+) littermates and the historical mean.

In summary, the ovalbumin challenge studies indicate that knockout mice deficient in the gene encoding PRO1079 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited a decreased ability to elicit an immunological response when challenged with the T-cell dependent OVA antigen. Thus, PRO1079 polypeptides or agonists thereof, would be useful for stimulating the immune system (such as T cell proliferation) and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, inhibitors (antagonists) of PRO1079 polypeptides would be useful for inhibiting the immune response and thus would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(e) Cardiovascular Phenotypic Analysis:

In the area of cardiovascular biology, phenotypic testing was performed to identify potential targets for the treatment of cardiovascular, endothelial or angiogenic disorders. One such phenotypic test included optic fundus photography and angiography to determine the retinal arteriovenous ratio (A/V ratio) in order to flag various eye abnormalities. An abnormal A/V ratio signals such systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders. Such eye abnormalities may include but are not limited to the following: retinal abnormality is retinal dysplasia, various retinopathies, restenosis, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal dysplasia congenita, Flynn-Aird syndrome,

Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinememia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

5 Procedure: A cohort of 4 wild type, 4 heterozygotes and 1 homozygote were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct ophthalmological changes, this test can detect retinal changes associated with
10 systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye.

Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according
15 to the fundus images with Kowa COMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). Many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic
20 observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions.

Results:

Fundus: One (-/-) (M-99) mouse exhibited retinal hemorrhage, preventing analysis of the artery-to-vein ratio.
Angiogram: One (-/-) mouse (M-99) exhibited retinal vascular leakage.

25 Such detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders such as retinal degeneration. Thus, antagonists of PRO1079 encoding genes would lead to similar pathological retinal changes, whereas agonists may be useful as therapeutic agents in the treatment of hypertension, atherosclerosis or other
30 ophthalmological disorders including retinal degeneration and diseases associated with this condition (as indicated above).

(f) *Bone Metabolism & Body Diagnostics/Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- 35 • DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 1 homozygote were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

DEXA: The single male (-/-) mouse available for analysis exhibited decreased total tissue mass and lean body mass when compared with its gender-matched (+/+) littermates and the historical means, whereas the female (-/-) mouse analyzed exhibited increased total tissue mass (TTM), total fat mass and percent total body fat (single (-/-) female mouse had 34% body fat).

The male (-/-) mice analyzed by DEXA exhibited notably decreased total tissue mass and lean body mass as well as decreased bone measurements when compared with their (+/+) littermates, suggestive of growth retardation in these mutants. These observations are consistent with the reduced viability shown in the knockout mice. This in conjunction with the observations of decreased body weight and length is indicative of growth retardation, a tissue wasting condition such as cachexia or other growth related disorders. Thus, PRO1079 polypeptides or agonists thereof would be useful in the treatment or prevention of growth disorders and/or decreased viability. It is interesting that the female (-/-) mouse showed signs of obesity with notable increased body fat.

66.16. Generation and Analysis of Mice Comprising DNA58727-1474 (UNQ553) Gene Disruptions

In these knockout experiments, the gene encoding PRO1110 polypeptides (designated as DNA58727-1474) (UNQ553) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_016969 ACCESSION:NM_016969 NID: gi 8393799 ref NM_016969.1 Mus musculus myeloid-associated differentiation marker (Myadm); protein reference: O35682 ACCESSION:O35682 NID: Mus musculus (Mouse). Myeloid-associated differentiation marker (Myeloid upregulated protein); the human gene sequence reference: NM_138373 Homo sapiens myeloid-associated differentiation marker (MYADM); the human protein sequence corresponds to reference: Q96S97 ACCESSION:Q96S97 NID: Homo sapiens (Human). Myeloid-associated differentiation marker (SB135).

The mouse gene of interest is Myadm (myeloid-associated differentiation marker), ortholog of human MYADM. Aliases include D7Wsu62e.

MYADM is a likely integral plasma membrane protein, consisting of eight transmembrane segments contained within two MARVEL domains. MARVEL domains are often found in lipid-associating proteins that participate in transport vesicle biogenesis (Pfam accession PF01284). MYADM is expressed in myeloid cells and is likely involved in myeloid differentiation (Pettersson et al, *J Leukoc Biol* 67(3):423-31 (2000); Cui et al, *Mol*

Biol Rep 28(3):123-38 (2001)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	11	33	16	60
Expected	15	30	15	60

Chi-Sq.= 4.24 Significance= 0.12003164 (hom/n)= 0.24 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_016969.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except bone and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.16.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA58727-1474 (UNQ553))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human myeloid-associated differentiation marker (MYADM) resulted in increased TNF-alpha, MCP-1, and IL-6 responses to LPS challenge in (-/-) mice. In addition, mutant (-/-) mice on a high fat diet exhibited a slightly enhanced glucose tolerance. The mutant (-/-) mice exhibited a decreased or absent startle response indicating deafness. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells,

virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

5 In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, 10 hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune 15 response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

20 *Acute Phase Response:*

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sublethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and 25 analyzed for the presence of TNFa, MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

The (-/-) mice exhibited increased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge when compared with their (+/+) littermates and the historical means.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding 30 PRO1110 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (TNF-alpha, MCP-1 and IL-6 production) when challenged with the LPS endotoxin indicating a pro-inflammatory response. TNF-alpha, MCP-1 and IL-6 contribute to the later stages of B cell activation. TNF-alpha is an important inflammatory mediator. In addition, TNF-alpha, MCP-1 and IL-6 play a critical role in inducing the acute phase response and 35 systemic inflammation. TNF-alpha can substitute for the membrane-bound signal in macrophage activation (thus serving as an effector molecule). This suggests that inhibitors or antagonists to PRO1110 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such

as AIDS sufferers. Accordingly, PRO1110 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(c) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Glucose Tolerance Test: The male mutant (-/-) mice on a high fat diet exhibited a slightly enhanced glucose tolerance when compared with their gender-matched (+/+) littermates.

In these studies the mutant (-/-) mice showed an increased or enhanced glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mice exhibited a slightly increased insulin sensitivity or the opposite phenotypic pattern of an impaired glucose homeostasis, and as such antagonists (inhibitors) to PRO1110 polypeptides or its encoding gene would be useful in the treatment of an impaired glucose homeostasis.

(d) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier

testing.

Prepulse inhibition of the acoustic startle reflex

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB + 120 dB - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

Results:

The knockout mutant (-/-) mice exhibited a decreased or absent startle response which is indicative of deafness.

66.17. Generation and Analysis of Mice Comprising DNA62377-1381-1 (UNQ561) Gene Disruptions

In these knockout experiments, the gene encoding PRO1122 polypeptides (designated as DNA62377-1381-1) (UNQ561) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_145834 ACCESSION:NM_145834 NID: gi 22003879 ref NM_145834.1 Mus musculus interleukin 17C (IL17c); protein reference: Q8K4C5 ACCESSION:Q8K4C5 NID: Mus musculus (Mouse). IL-17C; the human gene sequence reference: NM_013278 ACCESSION:NM_013278 NID: gi 27477078 ref NM_013278.3 Homo sapiens interleukin 17C (IL17C); the human protein sequence corresponds to reference: Q9P0M4 ACCESSION:Q9P0M4 NID: Homo sapiens (Human). Interleukin-17C precursor (IL-17C) (Cytokine CX2).

The mouse gene of interest is IL17c (interleukin 17C), ortholog of human IL17C. Aliases include IL-17C, CX2, IL-21, and cytokine CX2.

IL17C is a secreted protein that likely functions as a ligand for an interleukin-17 family receptor. Cells that express this cytokine have not been identified; however, IL17C stimulates release of tumor necrosis factor-alpha and IL-1beta from monocytic cell line THP-1. Moreover, IL17C induces neutrophilia and expression of interferon-gamma and interleukin-6 in lung airway, supporting a role for IL17C in immune function (Li et al, Proc Natl Acad Sci U S A 97(2):773-8 (2000); Hurst et al, J Immunol 169(1):443-53 (2002); Moseley et al, Cytokine Growth Factor Rev 14(2):155-74 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	34	13	65
Expected	16.25	32.5	16.25	65

Chi-Sq.= 2.59 Significance= 0.2738979 (hom/n)= 0.21 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_145834.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except liver; skeletal muscle; bone; stomach, small intestine, and colon; and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.17.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA62377-1381-1 (UNQ561))

10 (a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human interleukin 17C (IL17C) resulted in elevated mean serum levels of IgM serum immunoglobulins in the (-/-) mice. The mutant (-/-) mice also showed an increased in IL-6 response to LPS. Gene disruption was confirmed by Southern blot.

(b) Immunology Phenotypic Analysis

15 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

20 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

25 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

30 In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

35 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated

inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

The (-/-) mice exhibited an increased mean serum IgM level when compared with that of their (+/+) littermates and the historical medians.

Mutant (-/-) mice exhibited elevation of IgM serum immunoglobulins compared to their gender-matched (+/+) littermates. IgM immunoglobulins are the first to be produced in a humoral immune response for neutralization of bacterial toxins and are particularly important in activating the complement system. The observed phenotype suggests that the PRO1122 polypeptide is a negative regulator of inflammatory responses. These immunological abnormalities suggest that inhibitors (antagonists) of PRO1122 polypeptides would be important agents which could stimulate the immune system (such as T cell proliferation) and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1122 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

Acute Phase Response:

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sub-lethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNF α , MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

The (-/-) mice exhibited an increased mean serum IL-6 response to LPS challenge when compared with their (+/+) littermates and the historical means.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO1122 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (IL-6 production)

when challenged with the LPS endotoxin indicating a pro-inflammatory response. IL-6 contributes to the later stages of B cell activation playing a critical role in inducing the acute phase response and systemic inflammation. This suggests that inhibitors or antagonists to PRO1122 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1122 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

66.18. Generation and Analysis of Mice Comprising DNA58850-1495 (UNQ576) Gene Disruptions

In these knockout experiments, the gene encoding PRO1138 polypeptides (designated as DNA58850-1495) (UNQ576) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_144539 Mus musculus SLAM family member 7 (Slamf7); protein reference: Q8BHK6 ACCESSION:Q8BHK6 NID: Mus musculus (Mouse). Mus musculus adult male testis cDNA, RIKEN full-length enriched library, clone:4932702H22 product:SIMILAR TO 19A24 PROTEIN homolog (Mus musculus adult male testis cDNA, RIKEN full-length enriched library, clone:4932704K11 product:SIMILAR TO 19A24 PROTEIN homolog) (Mus musculus adult male aorta and vein cDNA, RIKEN full-length enriched library, clone:A530014C02 product:SIMILAR TO 19A24 PROTEIN homolog); the human gene sequence reference: NM_021181 Homo sapiens SLAM family member 7 (SLAMF7); the human protein sequence corresponds to reference: Q9NY08 ACCESSION:Q9NY08 NID: Homo sapiens (Human). 19A protein.

The mouse gene of interest is Slamf7 (SLAM family member 7), ortholog of human SLAMF7. Aliases include 19A, CS1, 19A24, CRACC, 4930560D03Rik, CD2-like receptor activating cytotoxic cells, novel Ly9, and novel LY9 (lymphocyte antigen 9) like protein.

SLAMF7 is a type I plasma membrane protein that functions as a homophilic receptor or cell adhesion molecule and is expressed primarily on natural killer cells, T-cells, and activated B-cells. The protein consists of two extracellular immunoglobulin-like domains, a transmembrane segment, and an 88-amino acid cytoplasmic domain. SLAMF7 likely plays a role in regulating NK cell cytolytic activity and lymphocyte adhesion (Kumaresan et al, *Mol Immunol* 39(1-2):1-8 (2002); Murphy et al, *Biochem J* 361(Pt 3):431-6 (2002); Bouchon et al, *J Immunol* 167(10):5517-21 (2001); Tovar et al, *Immunogenetics* 54(6):394-402 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	22	37	16	75
Expected	18.75	37.5	18.75	75

Chi-Sq= 1.63 Significance= 0.44263932 (hom/n)= 0.22 Avg. Litter Size= 10

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 2 through 6 were targeted (NCBI accession NM_144539.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.

5 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.18.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA58850-1495 (UNQ576))

(a) *OVERALL PHENOTYPIC SUMMARY:*

10 Mutation of the gene encoding the ortholog of human SLAM family member 7 (SLAMF7) resulted in an increase in the IL-6 response to LPS. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

15 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

20 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

25 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

30 In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

35 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and

inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

5 The following test was performed:

Acute Phase Response:

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sub-lethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNF α , MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

The (-/-) mice exhibited an increased mean serum IL-6 response to LPS challenge when compared with their (+/+) littermates and the historical means.

15 In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO1138 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (IL-6 production) when challenged with the LPS endotoxin indicating a pro-inflammatory response. IL-6 contributes to the later stages of B cell activation playing a critical role in inducing the acute phase response and systemic inflammation. This suggests that inhibitors or antagonists to PRO1138 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1138 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

66.19. Generation and Analysis of Mice Comprising DNA59586-1520 (UNQ604) Gene Disruptions

In these knockout experiments, the gene encoding PRO1190 polypeptides (designated as DNA59586-1520) (UNQ604) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_172506 Mus musculus biregional cell adhesion molecule-related/down-regulated by oncogenes (Cdon) binding protein (Boc); protein reference: Q8CE91
30
ACCESSION:Q8CE91 NID: Mus musculus (Mouse). Mus musculus 10 days neonate skin cDNA, RIKEN full-length enriched library, clone:4732455C11 product:biregional cell adhesion molecule-related/down-regulated by oncogenes (Cdon)binding protein, full insert sequence; the human gene sequence reference: NM_033254
35
ACCESSION:NM_033254 NID: gi 15147239 ref NM_033254.1 Homo sapiens brother of CDO (BOC); the human protein sequence corresponds to reference: Q9BWV1 ACCESSION:Q9BWV1 NID: Homo sapiens (Human). BROTHER OF CDO.

The mouse gene of interest is Boc (biregional cell adhesion molecule-related/down-regulated by

oncogenes (Cdon) binding protein), ortholog of human BOC (brother of CDO). Aliases include 4732455C11 and Biregional Cdon binding protein.

BOC is a type I plasma membrane protein that likely functions as a receptor subunit for cell-cell communication. The protein interacts with homolog CDON (cell adhesion molecule-related/down-regulated by oncogenes), N-cadherins, and M-cadherins in a cis fashion, forming a receptor complex at sites of cell-cell contact in myoblasts. During embryonic development, BOC is expressed in musculoskeletal and central nervous systems and in areas of proliferation and differentiation. BOC likely plays a role in muscle cell differentiation and transformation (Wegorzewska et al, *Mol Carcinog* 37(1):1-4 (2003); Mulieri et al, *Dev Dyn* 223(3):379-88 (2002); Kang et al, *EMBO J* 21(1-2):114-24 (2002); Kang et al, *Proc Natl Acad Sci U S A* 100(7):3989-94 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	30	20	68
Expected	17	34	17	68

Chi-Sq.= 1.3 Significance= 0.5220458 (hom/n)= 0.25 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_172506.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.19.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA59586-1520 (UNO604)

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human brother of CDO (BOC) resulted in two knockout mice exhibiting a systemic histiocytic storage disease affecting only the macrophages in several organs. Gene disruption was confirmed by Southern blot.

(b) *Pathology*

Gross: Two of the (-/-) mice examined (M-138 and F-139) exhibited an enlarged liver, spleen, and mesenteric lymph nodes.

Microscopic: Among the (-/-) mice analyzed, 2 (F-139 and M-138) exhibited a systemic histiocytic storage disease affecting only the macrophages in several organs. The liver, spleen, and mesenteric lymph nodes were the most affected histologically. The cytoplasm of the macrophages was markedly enlarged and contained predominantly clear vacuoles and less prominent fibrillar material. The clear vacuoles were the artifactual remnants of structures

containing material dissolved during the process required to prepare histological slides. The removed material presumably contained lipid predominantly. These lesions were characteristic of a group of genetic diseases known as lipid storage diseases.

66.20. Generation and Analysis of Mice Comprising DNA64896-1539 (UNQ642) Gene Disruptions

5 In these knockout experiments, the gene encoding PRO1272 polypeptides (designated as DNA64896-1539) (UNQ642) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_207531 Mus musculus RIKEN cDNA E030025L21 gene (E030025L21Rik); protein reference: Q8R3W7 ACCESSION:Q8R3W7 NID: Mus musculus (Mouse). RIKEN cDNA E030025L21 gene; the human gene sequence reference: NM_176813 Homo sapiens breast cancer
10 membrane protein 11 (BCMP11); the human protein sequence corresponds to reference: Q8TD06 ACCESSION:Q8TD06 NID: Homo sapiens (Human). Anterior gradient protein 3 (MLHS642) (Breast cancer membrane protein 11).

The mouse gene of interest is RIKEN cDNA E030025L21 gene, ortholog of human BCMP11 (breast cancer membrane protein 11). Aliases include Gm888, HAG3, hAG-3, and anterior gradient protein 3.

15 BCMP11 is a putative secreted protein expressed primarily in estrogen receptor-positive breast ductal carcinoma epithelial cells. The 166-amino acid protein contains a signal peptide but no other discernable conserved domain. BCMP11 is concentrated in cytoplasmic vesicles but is capable of interacting with glycosylphosphatidylinositol-anchored metastasis-associated protein C4.4A and extracellular alpha-dystroglycan (DAG-1). Moreover, BCMP11 is homologous with secreted *Xenopus laevis* proteins XAG-1 and XAG-2, further
20 supporting the function of BCMP11 as a secreted extracellular protein. BCMP11 may play a role in breast tumor cell growth or metastasis (Adam et al, *J Biol Chem* 278(8):6482-9 (2003); Fletcher et al, *Br J Cancer* 88(4):579-85 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are
25 intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
30 Observed	22	23	17	62
Expected	15.5	31	15.5	62

Chi-Sq.= 0.79 Significance= 0.67368 (hom/n)= 0.26 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

35 Description: Coding exons 3 through 7 were targeted (NCBI accession NM_207531.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in brain; spinal cord; eye; lung; and stomach, small intestine, and colon among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.20.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA64896-1539 (UNQ642))(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human breast cancer membrane protein 11 (BCMP11) resulted in the homozygous mutant mice exhibiting an increased mean serum glucose levels with an impaired glucose tolerance when compared with those of their gender-matched wild-type littermates and the historical means. In addition, impaired glucose tolerance was observed in the male mutants. Glucosuria and ketonuria were also evident in the (-/-) mice. The homozygous mutant mice also exhibited decreased bone mineral content and density measurements and decreased heart rates. Neurological analysis revealed numerous abnormalities, including impaired motor coordination and shaky behavior. The (-/-) mice exhibited diffuse abiotrophy of the cerebellum granule cell layer. The male (-/-) mice also showed testicular degeneration and the female (-/-) mice exhibited ovarian and uterine hypoplasia. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

Microscopic: The (-/-) mice exhibited diffuse abiotrophy of the cerebellum granule cell layer, characterized by a diffuse loss of granule cells and gliosis, resulting in thinning of both the granule cell layer and molecular cell layer of the cerebellum. Notably, there was sparing of Purkinje and Golgi cells and the granule cell layer of the cerebellar paraflocculus was less severely affected by gliosis and neuron loss. The male (-/-) mice exhibited small testes, testicular degeneration, and hypospermia. Evidence of degeneration in the seminiferous tubules was minimal and restricted to late stage spermatids and spermatozoa. However, almost no normal sperm were present in the epididymides or vas deferens, and degeneration and clumping of spermatozoa was a frequent finding. The female (-/-) mice exhibited ovarian and uterine hypoplasia, with the ovaries and uterus appearing juvenile. The mammary gland was represented by just a few ducts. Heart weights were increased in the (-/-) mice, but no histopathologic lesions were noted. The pancreatic islets of Langerhans in the mutants tended to be smaller than in the (+/+) controls and the distribution of alpha (glucagon) and beta (insulin) cells was altered. Normally, glucagon-producing islet cells are arranged around the periphery of the islets, but the glucagon cells in the mutants were evenly distributed throughout the islets.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Cardiology - Heart Rate*

Test Description: Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious systolic blood pressure.

30 Results

Heart Rate: The (-/-) mice exhibited decreased mean heart rates (male (-/-) > 2 SD below the mean; female (-/-) > 3 SD below the mean) when compared with that of their gender-matched (+/+) littermates and the historical mean, the difference being more notable in the females.

(d) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity

and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Blood Glucose Levels/Glucose Tolerance Test:

Both the male and female mutant (-/-) mice exhibited notably increased mean serum glucose levels when compared with that of their gender-matched (+/+) littermates and the historical means. In addition, the (-/-) mice exhibited impaired glucose tolerance at each of the intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Glucosuria and ketonuria was evident in the (-/-) mutant mice.

These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose homeostasis, and therefor PRO1272 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

(e) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

(1) *Circadian Test Description:*

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning

on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

5 Results:

Circadian: The (-/-) mice exhibited decreased ambulatory activity during both light phases and a decreased light-to-total activity ratio during home-cage activity testing. These results demonstrate an abnormal circadian rhythm and is suggestive of decreased activity or hypoactivity which is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO1272 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

10 (2) *Functional Observational Battery (FOB) Test*

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

15 Results:

Among the 8 (-/-) mice analyzed, 4 exhibited shaky behavior during the 1-minute observation period. In addition, rearing was absent in the (-/-) mice.

20 (3) *Inverted Screen Test Data:*

The Inverted Screen is used to measure motor strength/coordination. Untrained mice were placed individually on top of a square (7.5 cm x 7.5 cm) wire screen which was mounted horizontally on a metal rod. The rod was then rotated 180 degrees so that the mice were on the bottom of the screens. The following behavioral responses were recorded over a 1 min testing session: fell off, did not climb, and climbed up.

25 Results:

Genotype	Ratio Fell Down %		Ratio Climbed up %	
+/+ (n=8)	0/8	0	6/8	75
30 -/- (n=8)	1/8	13	1/8	13

WT Population Fell Down 3.62 Climbed Up 60.04

A motor strength deficit is apparent when there is a 50% point difference between (-/-) or (+/-) mice and (+/+) mice for the fell down response. 0/8 or 1/8 (-/-) or (+/-) mice not climbing indicates impaired motor coordination. 7/8 or 8/8 (-/-) or (+/-) mice climbing up indicates enhanced motor coordination.

35 The Inverted Screen Test is designed to measure basic sensory & motor observations:

Among the 8 (-/-) mice analyzed, only one (-/-) mouse climbed up the screen whereas 6/8 (+/+) mice climbed up. These results indicate an impaired motor strength in the mutants. These results are consistent with the observations in bone-related measurements as shown below.

(f) *Bone Metabolism & Body Diagnostics*

(1) Tissue Mass & Lean Body Mass Measurements - Dexa

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

5 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

10 Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

15 The (-/-) mice exhibited decreased mean body weight when compared with their gender-matched (+/+) littermates and the historical mean.

Fertility: The male (-/-) mouse produced no pups after 60 days of breeding and 4 matings.

(2) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

20 · DEXA for measurement of bone mineral density on femur and vertebra

· MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

25 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

30 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

35 DEXA: The male (-/-) mice exhibited decreased mean total tissue mass and lean body mass. Both the male and female (-/-) mice exhibited decreased mean bone mineral content, bone mineral content index, and bone mineral density in total body, femur, and vertebrae when compared with that of their gender-matched (+/+) littermates and the historical means.

Mutant (-/-) mice deficient in the gene encoding PRO1272 polypeptides show a phenotype consistent with

growth retardation and/or tissue wasting diseases marked by decreased mean total mass, lean body mass. These results are consistent to the observation of decreased mean body weight reported above. In addition, the mutant (-/-) mice exhibited decreased bone mineral content and density measurements suggestive of osteoporosis. Thus, antagonists or inhibitors of PRO1272 polypeptides or its encoding gene would mimic these abnormal metabolic related effects. On the other hand, PRO1272 polypeptides or agonists thereof would be useful in the prevention and/or treatment of such metabolic disorders as growth retardation, cachexia or other tissue wasting diseases as well as useful in the treatment of bone disorders associated with bone loss.

(g) *Adult skin cell proliferation:*

Procedure: Skin cells were isolated from 16 week old animals (2 wild type and 4 homozygotes). These were developed into primary fibroblast cultures and the fibroblast proliferation rates were measured in a strictly controlled protocol. The ability of this assay to detect hyper-proliferative and hypo-proliferative phenotypes has been demonstrated with p53 and Ku80. Proliferation was measured using Brdu incorporation.

Specifically, in these studies the skin fibroblast proliferation assay was used. An increase in the number of cells in a standardized culture was used as a measure of relative proliferative capacity. Primary fibroblasts were established from skin biopsies taken from wild type and mutant mice. Duplicate or triplicate cultures of 0.05 million cells were plated and allowed to grow for six days. At the end of the culture period, the number of cells present in the culture was determined using a electronic particle counter.

Results:

The female (-/-) mice exhibited a increased mean skin fibroblast proliferation rate when compared with their gender-matched (+/+) littermates.

Thus, homozygous mutant mice demonstrated a hyper-proliferative phenotype. As suggested by these observations, PRO1272 polypeptides or agonists thereof would be useful in decreasing abnormal cell proliferation.

66.21. Generation and Analysis of Mice Comprising DNA64903-1553 (UNQ655) Gene Disruptions

In these knockout experiments, the gene encoding PRO1286 polypeptides (designated as DNA64903-1553) (UNQ655) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: BC029863 ACCESSION:BC029863 NID:20987635 Mus musculus Mus musculus, clone MGC:36861 IMAGE:4460168; protein reference: Q8K2T4 ACCESSION:Q8K2T4 NID: Mus musculus (Mouse). Hypothetical protein; the human gene sequence reference: AY358935 Homo sapiens clone DNA64903 DSLR655 (UNQ655); the human protein sequence corresponds to reference: Q6UW78 Protein UNQ655/PRO1286 precursor.

The mouse gene of interest encodes "protein UNQ655/PRO1286 precursor" (UNQ655), ortholog of human UNQ655.

UNQ655 is a putative secreted protein, consisting of 93 amino acids. The protein contains a signal peptide but no other discernible conserved domain.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}

/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	34	0	55
Expected	13.75	27.5	13.75	55

5 Chi-Sq.= 38.76 Significance= 3.8315395E-9 (hom/n)= 0.0 Avg. Litter Size= 7

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession BC029863.1).

1. Wild-type Expression Panel: Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.21.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA64903-1553 (UNQ655))

(a) *OVERALL PHENOTYPIC SUMMARY:*

- 15 Mutation of the gene encoding the ortholog of human UNQ655 resulted in lethality of (-/-) mutants. The heterozygous mice exhibited decreased mean serum IgG2a levels. Gene disruption was confirmed by Southern blot.

(b) *Pathology*

- 20 Microscopic: Not tested due to embryonic lethality. At 12.5 days, there were 49 embryos observed: 18 (+/-) embryos, 8 (+/+) embryos, 22 resorption moles, and 1 inconclusive.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

Discussion related to embryonic developmental abnormality of lethality:

- 25 Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

30 (c) *Immunology Phenotypic Analysis*

- 35 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an

ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

Serum Imm. 2: The (+/-) mice exhibited a decreased mean serum IgG2a level when compared with that of their (+/+) littermates, the (+/+) mice within the project run, and the historical median.

The serum immunoglobulin isotyping assay showed decreased or reduced levels of IgG2a in the heterozygous (+/-) mice compared to their gender-matched littermate (+/+) controls.

The serum immunoglobulin isotyping assay revealed that heterozygous adults exhibited decreased serum IgG2a levels. Thus, heterozygotes showed an abnormally low serum immunoglobulins compared with the (+/+) littermates. Thus, the gene encoding PRO1286 polypeptides is essential for making immunoglobulins (or gamma globulins). Likewise, IgG2a immunoglobulins have neutralization effects and to a lesser extent are important for

activation of the complement system. These immunological abnormalities suggest that PRO1286 polypeptides or agonists thereof would be useful in stimulating the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, inhibitors (antagonists) of PRO1286 polypeptides would inhibit the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

66.22. Generation and Analysis of Mice Comprising DNA59218-1559 (UNQ664) Gene Disruptions

In these knockout experiments, the gene encoding PRO1295 polypeptides (designated as DNA59218-1559) (UNQ664) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: XM_485054 PREDICTED: Mus musculus congenital dyserythropoietic anemia, type I (human) (Cdan1); protein reference: XP_485054 congenital dyserythropoietic anemia, type I [Mus musculus]; the human gene sequence reference: NM_138477 Homo sapiens congenital dyserythropoietic anemia, type I (CDAN1); the human protein sequence corresponds to reference: Q8IWY9 ACCESSION:Q8IWY9 NID: Homo sapiens (Human). Codanin 1 (UNQ664/PRO1295).

The mouse gene of interest is Cdan1 (congenital dyserythropoietic anemia, type I [human]), ortholog of human CDAN1. Aliases include CDA1, CDAI, CDA-I, 1500015A01Rik, codanin, and codanin 1.

CDAN1 is a ubiquitously expressed protein located in the cytoplasm that likely functions as a structural protein, connecting the nuclear membrane with microtubules. CDAN1 may be involved in preserving nuclear membrane integrity. Mutations in CDAN1 can cause congenital dyserythropoietic anemias, a rare group of inherited red blood cell disorders associated with dysplastic changes in late erythroid precursors (Dgany et al, Am J Hum Genet 71(6):1467-74 (2002); Pielage et al, Dev Cell 5(6):841-51 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	32	0	53
Expected	13.25	26.5	13.25	53

Chi-Sq.= 47.76 Significance= 4.256456E-11 (hom/n)= 0.0 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 3 through 8 were targeted (NCBI accession XM_485054.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.22.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA59218-1559 (UNQ664))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human congenital dyserythropoietic anemia, type I (human) (CDAN1) resulted in lethality of (-/-) mutants. Lethality is likely due to a defect in erythropoiesis. UNQ675 is highly expressed in the CNS compared to other tissues. Gene disruption was confirmed by Southern blot.

(b) *Pathology*

Microscopic: Not tested due to embryonic lethality. At 12.5 days, 51 embryos were observed: 23 (+/-) embryos, 15 (+/+) embryos, 9 resorptions, and 4 to-be-determined.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

Discussion related to embryonic developmental abnormality of lethality:

Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

66.23. Generation and Analysis of Mice Comprising DNA59588-1571 (UNQ675) Gene Disruptions

In these knockout experiments, the gene encoding PRO1309 polypeptides (designated as DNA59588-1571) (UNQ675) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_028880 Mus musculus leucine rich repeat transmembrane neuronal 1 (Lrrtm1); protein reference: Q8K377 ACCESSION:Q8K377 NID: Mus musculus (Mouse). Lrrtm1 protein (Mus musculus 0 day neonate eyeball cDNA, RIKEN full-length enriched library, clone:E130010021 product:hypothetical RNI-like structure containing protein, full insert sequence) (Mus musculus 0 day neonate eyeball cDNA, RIKEN full-length enriched library, clone:E130012A05 product:hypothetical RNI-like structure containing protein, full insert sequence) (Leucine-rich repeat transmembrane neuronal 1 protein); the human gene sequence reference: NM_178839 Homo sapiens leucine rich repeat transmembrane neuronal 1 (LRRTM1); the human protein sequence corresponds to reference: Q86UE6 ACCESSION:Q86UE6 NID: Homo sapiens (Human). LRRTM1 protein (DFLL675).

The mouse gene of interest is Lrrtm1 (leucine rich repeat transmembrane neuronal 1), ortholog of human LRRTM1. Aliases include 4632401D06Rik, leucine-rich repeat transmembrane neuronal 1, DFLL675, and FLJ32082.

LRRTM1 is a putative integral plasma membrane protein expressed primarily in the nervous system that likely functions as a cell adhesion molecule or receptor. The protein consists of a signal peptide, several leucine-rich repeats, and a transmembrane segment. LRRTM1 may play a role in development and maintenance of the nervous system (Lauren et al, Genomics 81(4):411-21 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{hnd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are

intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
5 Observed	21	46	15	82
Expected	20.5	41	20.5	82

Chi-Sq.= 0.71 Significance= 0.7011734 (hom/n)= 0.23 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

10 Description: Coding exon 2 was targeted (NCBI accession NM_028880.2).

1. Wild-type Expression Panel: Expression of the target gene was detected only in brain, spinal cord, eye, and adipose among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

15 66.23.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA59588-1571 (UNQ675))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human leucine rich repeat transmembrane neuronal 1 (LRRTM1) resulted in increased body fat in (-/-) and (+/-) mice. In addition, the mutant (-/-) mice exhibited decreased median ambulatory counts during circadian rhythm testing. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

35 Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Circadian Test Description:

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The (-/-) mice exhibited decreased median ambulatory counts during both dark periods during home-cage activity testing compared with their gender-matched (+/+) littermates and the historical mean.

These results demonstrate an abnormal circadian rhythm and is suggestive of decreased activity or hypoactivity which is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO1309 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

(c) Bone Metabolism & Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImusTM Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

DEXA: Both the male and female (+/-) and (-/-) mice exhibited increased mean percent total body fat and total fat mass when compared with their gender-matched (+/+) littermates and the historical means, the difference being more notable in the females. The female (-/-) mice also exhibited notably increased mean total tissue mass.

These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with obesity. Thus, PRO1309 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be important in the prevention and/or treatment of obesity.

66.24. Generation and Analysis of Mice Comprising DNA60608-1577 (UNQ682) Gene Disruptions

In these knockout experiments, the gene encoding PRO1316 polypeptides (designated as DNA60608-1577) (UNQ682) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_020265 Mus musculus dickkopf homolog 2 (Xenopus laevis) (Dkk2); protein reference: Q9QYZ8 Dickkopf related protein-2 precursor (Dkk-2) (Dickkopf-2) (mDkk-2) gi|6272205|emb|CAB60110.1| dickkopf-2 [Mus musculus]; the human gene sequence reference: NM_014421 Homo sapiens dickkopf homolog 2 (Xenopus laevis) (DKK2); the human protein sequence corresponds to reference: Q9UBU2 ACCESSION:Q9UBU2 NID: Homo sapiens (Human). Dickkopf related protein-2 precursor (Dkk-2) (Dickkopf-2) (hDkk-2).

The mouse gene of interest is Dkk2 (dickkopf homolog 2 [Xenopus laevis]), ortholog of human DKK2. Aliases include DKK-2, dickkopf 2, mRNA for dickkopf-2 (dkk-2 gene), dickkopf homolog 1 (Xenopus laevis), Dickkopf gene 2, and dickkopf (Xenopus laevis) homolog 2.

DKK2 is a secreted protein that functions as a ligand for coreceptors of the canonical Wnt/beta-catenin signaling pathway. In the absence of coreceptor KREMEN2 (kringle containing transmembrane protein 2), DKK2 activates Wnt signaling by binding with coreceptor LRP6 (low density lipoprotein receptor-related protein 6). However, in the presence of KREMEN2, DKK2 inhibits Wnt signaling by binding with KREMEN2 (Mao and Niehrs, *Gene* 302(1-2):179-83 (2003); Brott and Sokol, *Mol Cell Biol* 22(17):6100-10 (2002); Li et al, *J Biol Chem* 277(8):5977-81 (2002); Krupnik et al, *Gene* 238(2):301-13 (1999)). DKK2 is involved in development (Monaghan et al, *Mech Dev* 87(1-2):45-56 (1999); Ang et al, *Gene Expr Patterns* 4(3):289-95 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	43	19	80
Expected	20	40	20	80

Chi-Sq.= 3.62 Significance= 0.16365415 (hom/n)= 0.26 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_020265.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except spinal cord, thymus, and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.24.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA60608-1577 (UNQ682))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human dickkopf homolog 2 (Xenopus laevis) (DKK2)

resulted in the homozygous mutant mice exhibiting corneal epithelialization with underdeveloped eyelids and agenesis of the Harderian gland, resulting in impaired vision in the mutants. All eight of the (-/-) mice exhibited abnormalities of the eye, including 6 (-/-) mice exhibiting palpebral closure. Gene disruption was confirmed by Southern blot.

(b) *Pathology*

- 5 Gross: All eight (-/-) mice exhibited severe corneal epidermidalization, characterized by thickening of the corneal stroma and scarring that blocked the vision of the mutants. The eyelids of the (-/-) mice were also underdeveloped, resulting in incomplete closure of the eyelids. Some appeared to have smaller than normal eyes. Both eyelids were notably hypoplastic and the Harderian glands were not visible upon gross examination of the (-/-) mice.
- 10 Microscopic: The (-/-) mice exhibited corneal epithelialization with underdeveloped eyelids and agenesis of the Harderian gland, resulting in impaired vision in the mutants. The (-/-) mice exhibited diffuse metaplasia of the cornea and sclera, characterized by diffuse fibrosis of the collagenous stroma and keratinizing hyperkeratosis of the surface epithelium with multifocal chronic-active keratitis and ulceration. Multifocally, there were sebaceous glands and hair follicles in the cornea and sclera. These changes were more severe in the male mutants than in the females. The (-/-) mice also exhibited agenesis of the Harderian gland. Although intraorbital lacrimal glands were
- 15 present in some sections, the Harderian gland was uniformly absent and the eyelids were severely hypoplastic in all mutant mice.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Cardiovascular Phenotypic Analysis:*

- 20 In the area of cardiovascular biology, phenotypic testing was performed to identify potential targets for the treatment of cardiovascular, endothelial or angiogenic disorders. One such phenotypic test included optic fundus photography and angiography to determine the retinal arteriovenous ratio (A/V ratio) in order to flag various eye abnormalities. An abnormal A/V ratio signals such systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders. Such eye abnormalities may include but
- 25 are not limited to the following: retinal abnormality is retinal dysplasia, various retinopathies, restenosis, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome,
- 30 Alstom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotidemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease,
- 35 mucopolysaccharidoses, homocystinuria, or mannosidosis.

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal

injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct ophthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye.

5 Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). Many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal
10 degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions.

Results:

15 Fundus: All 8 (-/-) mice exhibited severe corneal epidermidalization, characterized by thickening of the corneal stroma and scarring that blocked the vision of the mutants. The eyelids of the (-/-) mice were also underdeveloped, resulting in incomplete closure of the eyelids. Therefore, the artery-to-vein ratio could not be measured in the mutants.

20 Angiogram: Only 1 of the (-/-) mice was successfully analyzed. No notable posterior chamber anomaly was observed.

66.25. Generation and Analysis of Mice Comprising DNA58743-1609 (UNQ719) Gene Disruptions

In these knockout experiments, the gene encoding PRO1383 polypeptides (designated as DNA58743-1609) (UNQ719) was disrupted. The gene specific information for these studies is as follows: the mutated mouse
25 gene corresponds to nucleotide reference: NM_177735 Mus musculus hypothetical protein C130036G08 (C130036G08); protein reference: Q6NXM3 ACCESSION:Q6NXM3 NID: Mus musculus (Mouse). Hypothetical protein C130036G08; the human gene sequence reference: NM_152913 ACCESSION:NM_152913 NID: gi 23097273 refNM_152913.1 Homo sapiens hypothetical protein DKFZp761L1417 (DKFZp761L1417); the human protein sequence corresponds to reference: Q8N0W9 ACCESSION:Q8N0W9 NID: Homo sapiens (Human).
30 Similar to QNR-71 protein (Hypothetical protein).

The mouse gene of interest is "hypothetical protein C130036G08," ortholog of human "hypothetical protein DKFZp761L1417." Aliases include C130036G08 and DKFZp761L1417.

Hypothetical protein DKFZp761L1417 is a putative type I integral plasma membrane protein, containing a signal peptide, a PKD (repeats in polycystic kidney disease 1 [PKD1] and other proteins) domain (SMART
35 accession SM00089), and a transmembrane segment. PKD domains are likely involved in protein-protein or protein-carbohydrate interactions, suggesting that hypothetical protein DKFZp761L1417 functions as a cell adhesion molecule or signal-transducing receptor.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells.

The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

5		<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
	Observed	15	44	19	78
	Expected	19.5	39	19.5	78

Chi-Sq.= 1.42 Significance= 0.4916442 (hom/n)= 0.27 Avg. Litter Size= 10

Mutation Information

10 Mutation Type: Homologous Recombination (standard)

Description: Coding exons 3 through 5 were targeted (NCBI accession NM_177735.3).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except liver, skeletal muscle, and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

15

66.25.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA58743-1609 (UNQ719))

(a) OVERALL PHENOTYPIC SUMMARY:

20 Mutation of the gene encoding the ortholog of human "hypothetical protein DKFZp761L1417" resulted in the homozygous mutant mice exhibiting decreased locomotor activity or mild hypoactivity during open field testing when compared with the level for their wild-type littermates and the historical mean. UNQ719 shows high expression in the CNS compared to other tissues. Gene disruption was confirmed by Southern blot.

(b) Phenotypic Analysis: CNS/Neurology

25 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

35

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Open field test:

Several targets of known drugs have exhibited phenotypes in the open field test. These include knockouts of the serotonin transporter, the dopamine transporter (Giros et al., Nature. 1996 Feb 15;379(6566):606-12), and the GABA receptor (Homanics et al., Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):4143-8). An automated open-field assay was customized to address changes related to affective state and exploratory patterns related to learning. First, the field (40 X 40 cm) was selected to be relatively large for a mouse, thus designed to pick up changes in locomotor activity associated with exploration. In addition, there were 4 holes in the floor to allow for nose-poking, an activity specifically related to exploration. Several factors were also designed to heighten the affective state associated with this test. The open-field test is the first experimental procedure in which the mice are tested, and the measurements that were taken were the subjects' first experience with the chamber. In addition, the open-field was brightly lit. All these factors will heighten the natural anxiety associated with novel and open spaces. The pattern and extent of exploratory activity, and especially the center-to-total distance traveled ratio, may then be able to discern changes related to susceptibility to anxiety or depression. A large arena (40 cm x 40 cm, VersaMax animal activity monitoring system from AccuScan Instruments) with infrared beams at three different levels was used to record rearing, hole poke, and locomotor activity. The animal was placed in the center and its activity was measured for 20 minutes. Data from this test was analyzed in five, 4-minute intervals. The total distance traveled (cm), vertical movement number (rearing), number of hole pokes, and the center to total distance ratio were recorded.

The propensity for mice to exhibit normal habituation responses to a novel environment is assessed by determining the overall change in their horizontal locomotor activity across the 5 time intervals. This calculated slope of the change in activity over time is determined using normalized, rather than absolute, total distance traveled. The slope is determined from the regression line through the normalized activity at each of the 5 time intervals. Normal habituation is represented by a negative slope value.

Results:

A notable difference was observed during open field activity testing. The (-/-) mice exhibited a decreased median sum total distance traveled. Thus, knockout mice demonstrated a phenotype consistent with depression, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO1383 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

66.26. Generation and Analysis of Mice Comprising DNA71159-1617 (UNQ721) Gene Disruptions

In these knockout experiments, the gene encoding PRO1384 polypeptides (designated as DNA71159-1617) (UNQ721) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019985 Mus musculus C-type lectin-like receptor 2 (Clec2); protein reference: Q9JL99 ACCESSION: Q9JL99 NID: Mus musculus (Mouse). C-TYPE LECTIN-LIKE RECEPTOR 2; the human gene sequence reference: NM_016509 ACCESSION: NM_016509 NID: 7706060 Homo sapiens Homo sapiens C-type lectin-like receptor-2 (LOC51266); the human protein sequence corresponds to reference: Q9P126 ACCESSION: Q9P126 NID: Homo sapiens (Human). C-TYPE LECTIN-LIKE RECEPTOR-2. The mouse gene of interest is Clec2 (C-type lectin-like receptor 2), ortholog of human CLEC2. Aliases include Clec-2,

mCLEC-2, 1810061I13Rik, PRO1384, and QDED721.

CLEC2 is a type II integral plasma membrane protein that likely functions as a receptor. CLEC2 consists of a signal anchor and a C-type lectin domain, which binds with carbohydrate residues. CLEC2 is expressed in liver and in myeloid and natural killer cells. CLEC2 may play a role in signal transduction and immunity (Colonna et al, *Eur J Immunol* 30(2):697-704 (2000); Sobanov et al, *Eur J Immunol* 31(12):3493-503 (2001)).

- 5 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	43	3	62
Expected	15.5	31	15.5	62

Chi-Sq.= 10.34 Significance= 0.0056845685 (hom/n)= 0.12 Avg. Litter Size= 8

15 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_019985.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle; bone; stomach, small intestine, and colon; heart; and adipose.
- 20 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.26.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA71159-1617 (UNQ721))

(a) *OVERALL PHENOTYPIC SUMMARY:*

- 25 Mutation of the gene encoding the ortholog of human C-type lectin-like receptor 2 (CLEC2) resulted in greatly reduced viability of (-/-) mutants. Genetic data indicate that this mutation resulted in greatly reduced viability of the homozygous mutants. Microscopic analysis revealed numerous brain defects including mild-to-moderate congestion and hemorrhage in the diencephalon and vestibulocochlear ganglion of the homozygous embryos. The 2 surviving female homozygous mutant mice exhibited signs of anemia and decreased serum cholesterol, heart rate, and blood pressure. The mutants also exhibited an increased mean percentage of CD4
- 30 cells in the peripheral blood. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

General Observations: Reduced viability of the (-/-) mice was observed. All but 2 of the (-/-) mice were dead at the time of genotyping. Thus, high embryonic and prenatal lethality was observed.

- Microscopic: At 12.5 days there were 45 embryos observed: 11 (-/-) embryos, 18 (+/-) embryos, 11 (+/+) embryos, 3 resorption moles, and 2 inconclusive. The (-/-) embryos available for analysis exhibited mild-to-moderate brain (diencephalon) and vestibulocochlear ganglion congestion and hemorrhage. There were multiple foci of congestion and hemorrhage detected in the diencephalon of all 4 (-/-) embryos examined and unilaterally in the vestibulocochlear ganglion of 2/4 12.5 day (-/-) embryos. In addition, an increased number of dilated capillaries
- 35

were observed in the affected areas of the developing brains. In addition, circulating blood cells were found throughout the embryos especially the fetal liver. Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Cardiology - Blood Pressure/Heart Rate*

5 Test Description: Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious systolic blood pressure.

Results

Blood Pressure: The 2 surviving (-/-) mice exhibited decreased mean systolic blood pressure when compared with that of their gender-matched (+/+) littermates and the historical mean.

10 Heart Rate: The 2 surviving (-/-) mice exhibited a decreased mean heart rate (~ 1-2 SD below the historic mean) when compared with that of their gender-matched (+/+) littermates and the historical mean.

(d) *Phenotypic Analysis: Cardiology*

15 In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides.

Blood Lipids

20 Procedure: A cohort of 4 wild type, 4 heterozygotes and 2 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

25 Blood Chemistry: The 2 surviving female (-/-) mice (F-104 and F-133) exhibited a decreased mean serum cholesterol level when compared with that of their gender-matched (+/+) littermates and the historical mean.

30 As summarized above, the (-/-) mice exhibited notably decreased mean serum cholesterol levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO1384 gene resulted in hypocholesteremia which could lead to defective membrane formation and/or function.

(e) *Immunology Phenotypic Analysis*

35 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different

biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

(1) *Hematology Analysis:*

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

Results:

Hematology: The 2 surviving (-/-) mice (F-104 and F-133) exhibited a decreased mean red blood cell count, hemoglobin concentration, and hematocrit level when compared with the levels for their (+/+) littermates and the historical means.

These results are related to a phenotype associated with anemia. Thus, PRO1384 polypeptides, agonists thereof or the encoding gene for PRO1384 polypeptides must be essential for normal red blood cell production and as such would be useful in the treatment of blood disorders associated with anemia or a low hematocrit.

(2) *Flourescence-activated cell-sorting (FACS) Analysis*

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 2 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

5 In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

10 The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

15 FACS3: The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by an increased mean percentage of CD4 cells when compared with that of their (+/+) littermates and the historical mean.

20 Thus, knocking out the gene which encodes PRO1384 polypeptides causes an increase in the T cell population. From these observations, PRO1384 polypeptides or the gene encoding PRO1384 appears to act as a negative regulator of T cell proliferation. Thus, antagonists (inhibitors) of PRO1384 polypeptides would mimic this phenotype and would be beneficial in enhancing T cell proliferation.

66.27. Generation and Analysis of Mice Comprising DNA73401-1633 (UNQ737) Gene Disruptions

25 In these knockout experiments, the gene encoding PRO1431 polypeptides (designated as DNA73401-1633) (UNQ737) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_175684 Mus musculus FCH and double SH3 domains 1 (Fchsd1); protein reference: Q6PFY1 ACCESSION:Q6PFY1 NID: Mus musculus (Mouse). FCH and double SH3 domains 1; the human gene sequence reference: NM_033449 Homo sapiens FCH and double SH3 domains 1 (FCHSD1); the human protein sequence corresponds to reference: Q86WN1 ACCESSION:Q86WN1 NID: Homo sapiens (Human). FLJ00007-like protein.

30 The mouse gene of interest is Fchsd1 (FCH and double SH3 domains 1), ortholog of human FCHSD1. Aliases include A030002D08Rik and FLJ00007.

35 FCHSD1 is a putative cytoplasmic protein, consisting of a Fes/CIP4 (Fes tyrosine kinase/Cdc42-interacting protein) homology domain, two SH3 (src homology-3) domains, and a proline-rich C terminus (Kato and Kato, *Int J Mol Med* 13(5):749-54 (2004)). FES-CIP4 homology domain binds with tubulin (Takahashi et al, *J Biol Chem* 278(49):49129-33 (2003); Laurent et al, *Mol Cell Biol* 24(21):9351-8 (2004)). SH3 domains likely mediate processes such as increasing the local concentration proteins, determining the subcellular location of proteins, and mediating assembly of large multiprotein complexes (InterPro accession IPR001452). Thus, FCHSD1 may function as a docking protein for processes involving cytoskeletal rearrangement.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	38	19	78
Expected	19.5	39	19.5	78

Chi-Sq.= 0.9 Significance= 0.63762814 (hom/n)= 0.22 Avg. Litter Size= 9

10 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 7 were targeted (NCBI accession NM_175684.3).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone.

15 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.27.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA73401-1633 (UNQ737))

(a) *OVERALL PHENOTYPIC SUMMARY:*

20 Mutation of the gene encoding the ortholog of human FCH and double SH3 domains 1 (FCHSD1) resulted in the mutant (-/-) mice exhibiting elevated mean serum glucose levels. Male knockout (-/-) mice also exhibited increased fat percentages and increased fat mass (g) as well as female (-/-) mice showed a decreased femur bone mineral density and total body bone mineral density. In addition, the male (-/-) mice showed a decreased mean systolic blood pressure. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: Metabolism -Blood Chemistry*

25 In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes.

Results:

30 Blood Chemistry: The (-/-) mice exhibited a notably increased mean serum glucose levels when compared with their gender-matched (+/+) littermates and the historical means. However, glucose tolerance testing was normal.

As summarized above, the (-/-) mice exhibited increased mean serum glucose levels suggesting abnormal glucose metabolism or a pre-diabetic condition.

(c) *Cardiology - Blood Pressure/Heart Rate*

35 Test Description: Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious systolic blood pressure.

Results.

Blood Pressure: The male (-/-) mice exhibited decreased mean systolic blood pressure when compared with that of their gender-matched (+/+) littermates and the historical mean.

(d) Bone Metabolism & Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

DEXA: The male (-/-) mice exhibited increased mean percent total body fat and total fat mass when compared with their gender-matched (+/+) littermates and the historical means. The female (-/-) mice exhibited decreased femur bone mineral density and total bone mineral density.

These studies suggest that mutant male (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with obesity. Thus, PRO1431 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be important in the prevention and/or treatment of obesity. The female knockout mice exhibited a negative bone phenotype associated with decreased bone mineral density measurements which could be due to osteoporosis. Thus, PRO1431 polypeptides or agonists thereof would be useful in the treatment of such bone disorders that are characterized by decreased bone mineral density.

66.28. Generation and Analysis of Mice Comprising DNA68818-2536 (UNQ739) Gene Disruptions

In these knockout experiments, the gene encoding PRO1434 polypeptides (designated as DNA68818-2536) (UNQ739) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_177033 Mus musculus RIKEN cDNA A930041G11 gene (A930041G11Rik); protein reference: Q8C8N3 ACCESSION:Q8C8N3 NID: Mus musculus (Mouse). Hypothetical von Willebrand factor; the human gene sequence reference: NM_198570 Homo sapiens PSST739 (UNQ739); the human protein sequence corresponds to reference: Q6UXE2 ACCESSION:Q6UXE2 NID: Homo sapiens (Human). PSST739.

The mouse gene of interest is RIKEN cDNA A930041G11 gene, ortholog of human UNQ739. Aliases

include PSST739.

UNQ739 is a putative secreted protein, containing a signal peptide, and two tandem von Willebrand factor type C (VWC) domains. VWC domains are found in numerous plasma proteins as well as intracellular proteins. VWC domains likely participate in oligomerization or complex formation (Pfam accession 00093).

5 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

10	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	34	27	86
Expected	21.5	43	21.5	86
Chi-Sq.= 1.21 Significance= 0.5460744 (hom/n)= 0.27 Avg. Litter Size= 10				

Mutation Information

15 Mutation Type: Homologous Recombination (standard)

Description: The exon preceding coding exon 1 and coding exon 1 were targeted (NCBI accession AK033944.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in brain, spinal cord, eye, thymus, spleen, lung, and heart among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

20

66.28.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA68818-2536 (UNQ739))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of a human putative secreted protein (UNQ739) resulted in enhanced sensorimotor gating/attention in (-/-) mice. The homozygous mutant mice exhibited enhanced sensorimotor gating/attention at 3 of 4 prepulse intensities when compared with the level for their wild-type littermates and the historical means. In addition, the (-/-) mice exhibited a trend in decreased alkaline phosphatase levels. Hematology revealed decreased mean total white blood cell count and absolute lymphocyte counts in the (-/-) mice. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Phenotypic Analysis: CNS/Neurology*

30 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood

disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Prepulse inhibition of the acoustic startle reflex

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB + 120 dB - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

Results:

PPI: The (-/-) mice exhibited notably increased median prepulse inhibition during pp4, pp8, and pp12 when compared with the levels for their (+/+) littermates and the historical means, suggesting enhanced sensorimotor gating/attention in the mutants.

(c) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating

cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

(1) *Hematology Analysis:*

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

Results:

Hematology: The (-/-) mice exhibited decreased mean total white blood cell and absolute lymphocyte counts when compared with those of their (+/+) littermates and the historical means.

These results indicate that mutant (-/-) mice have immunological abnormalities compared with their wild-type littermates. The (-/-) mice showed a decreased absolute lymphocyte count indicative of abnormal adaptive immunity. Thus, PRO1434 polypeptides must be essential for maintaining a normal immunological profile especially for adaptive immunity.

66.29. Generation and Analysis of Mice Comprising DNA61185-1646 (UNQ746) Gene Disruptions

In these knockout experiments, the gene encoding PRO1475 polypeptides (designated as DNA61185-1646) (UNQ746) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_026651 ACCESSION:NM_026651 NID:22267451 Mus musculus Mus musculus RIKEN cDNA 4930467B06 gene (4930467B06Rik); protein reference: Q91X88 ACCESSION:Q91X88 NID: Mus musculus (Mouse). O-mannosyl N-acetylglucosaminyltransferase; the human gene sequence reference: NM_017739 ACCESSION:NM_017739 NID:8923252 Homo sapiens Homo sapiens O-linked mannosyl N-acetylglucosaminyltransferase (FLJ20277); the human protein sequence corresponds to reference: Q9N9F9 ACCESSION:Q9N9F9 NID: Homo sapiens (Human). CDNA FLJ20277 FIS, CLONE HEP02567.

The mouse gene of interest is RIKEN cDNA 4930467B06 gene, ortholog of human FLJ20277 (O-linked mannosyl N-acetylglucosaminyltransferase). Aliases include 0610016I07Rik, O-mannosyl N-acetylglucosaminyltransferase, MEB, GnT1.2, MGAT1.2, POMGNT1, and UDP-GlcNAc.

FLJ20277 is a Golgi membrane glycosyltransferase that catalyzes the addition of N-acetylglucosamine (GlcNAc) to the alpha-linked terminal mannose (Man) of O-mannosylated proteins (Zhang et al, Biochem J 361 (Pt 1):153-62 (2002); Schacter, Biochim Biophys Acta 1573(3):292-300 (2002)). This enzyme participates in O-mannosyl glycan synthesis, which occurs primarily brain, nerve and skeletal muscle (Yoshida et al, Dev Cell 1(5):717-24 (2001)). Mutations in FLJ20277 cause muscle-eye-brain diseases, an autosomal recessive disorder characterized by congenital muscular dystrophy, brain malformation, and ocular abnormalities (Vervoort et al, Ann Neurol 56(1):143-8 (2004); Many et al, Biochem Biophys Res Commun 306(1):93-7 (2003); Taniguchi et al, Hum Mol Genet 12(5):527-34 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	39	13	73
Expected	18.25	36.5	18.25	73

Chi-Sq.= 10.29 Significance= 0.0058284746 (hom/n)= 0.18 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: The exon preceding coding exon 1 and coding exons 1 through 5 were targeted (NCBI accession NM_026651.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in brain and spinal cord among 13 adult tissues samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.29.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA61185-1646 (UNQ746))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human O-linked mannose beta1,2-N-acetylglucosaminyltransferase (FLJ20277) resulted in developmental malformation of the brain in (-/-) mice. Retinal vessel disorganization, peripheral retinal degeneration, and microaneurysms were observed in the homozygous mutant mice upon fundus examination. Microscopic analysis confirmed the retinal abnormalities and revealed developmental malformation of the brain in the mutants. In addition, both the male and female (-/-) mice exhibited an impaired glucose tolerance when compared with their gender-matched wild-type littermates and the historical means. The (-/-) mice were smaller than their (+/+) littermates and showed decreased mean body weight and length. Radiological observations showed abnormal bone-related measurements related to osteoporosis. Several neurological abnormalities were also observed in the knockout (-/-) mice. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) Pathology

Microscopic: The (-/-) mice exhibited mild-to-moderate multifocal developmental malformation of the brain. There was widespread evidence of defective neuronal migration in the brain as shown by the retention of nests of external granular cell neurons in the cerebellum and associated fusion of cerebellar folia, the scalloped appearance of the ventral arm of the dentate gyrus of the hippocampus, the diffuse disorganization of neurons and loss of neuronal cell layers in the cerebral cortex, and the fusion of both hemispheres in the area of the dorsal median sulcus. Frequently, mild dilatation of the lateral ventricles was also observed. The (-/-) mice also exhibited diffuse retinal atrophy, characterized by a general reduction in ganglion cell numbers, more severely at the periphery, with associated thinning of the inner and outer nuclear layers of the retina. The retinal vessels frequently lay on the surface of the retina, in direct contact with the vitreous, instead of being embedded in the ganglion cell layer as normal. In some eyes, retinoschisis is evident within the peripheral inner nuclear layer.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) Cardiovascular Phenotypic Analysis:

In the area of cardiovascular biology, phenotypic testing was performed to identify potential targets for the treatment of cardiovascular, endothelial or angiogenic disorders. One such phenotypic test included optic fundus photography and angiography to determine the retinal arteriovenous ratio (A/V ratio) in order to flag various eye abnormalities. An abnormal A/V ratio signals such systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders. Such eye abnormalities may include but are not limited to the following: retinal abnormality is retinal dysplasia, various retinopathies, restenosis, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alston's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedrich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct ophthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye.

Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant

progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). Many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wild-type (+/+) littermates would be indicative of such pathological conditions.

Results:

Fundus: The (-/-) mice exhibited optic nerve fiber layer striation and aggregation, retinal vessel disorganization, and peripheral retinal degeneration. One (-/-) mouse (F-174) also exhibited bulging eyes, suggesting increased intraocular pressure.

Angiogram: The (-/-) mice exhibited severe retinal vessel disorganization, microaneurysms, and retinal capillary leakage.

In summary, in this study, (-/-) mice showed ophthalmological abnormalities which would lead to abnormal retinal vessels and retinal degeneration when compared with their (+/+) littermates. In summary, by knocking out the gene identified as DNA61185-1646 encoding PRO1475 polypeptides, homozygous mutant progeny exhibit phenotypes which are associated with optic nerve and retinal artery abnormalities. Such detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders such as retinal degeneration and even blindness. Thus, antagonists of PRO1475 encoding genes would lead to similar pathological retinal changes, whereas agonists would be useful as therapeutic agents in the treatment of hypertension, atherosclerosis or other ophthalmological disorders including retinal degeneration and diseases associated with this condition (as indicated above).

(d) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Circadian Test Description:

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The female (-/-) mice exhibited decreased median ambulatory counts especially during the light phase when compared with the number for their gender-matched (+/+) littermates and the historical mean. These results demonstrate an abnormal circadian rhythm. Home-cage activity testing is also suggestive of decreased activity or hypoactivity which is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO1475 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

Inverted Screen Testing:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Inverted Screen Test Data:

The Inverted Screen is used to measure motor strength/coordination. Untrained mice were placed individually on top of a square (7.5 cm x 7.5 cm) wire screen which was mounted horizontally on a metal rod. The rod was then rotated 180 degrees so that the mice were on the bottom of the screens. The following behavioral responses were recorded over a 1 min testing session: fell off, did not climb, and climbed up.

Results:

Genotype	Ratio Fell Down %		Ratio Climbed up %	
+/+ (n=8)	1/8	12.5%	0/8	0
-/- (n=8)	4/8	50%	0/8	0

A motor strength deficit is apparent when there is a 50% point difference between (-/-) or (+/-) mice and (+/+) mice for the fell down response. 0/8 or 1/8 (-/-) or (+/-) mice not climbing indicates impaired motor coordination. 7/8 or 8/8 (-/-) or (+/-) mice climbing up indicates enhanced motor coordination.

The Inverted Screen Test is designed to measure basic sensory & motor observations:

Among the 8 (-/-) mice analyzed, all 4 (-/-) mice fell off in the screen whereas 1/8 (+/+) mice fell off suggesting an impaired motor coordination in the mutants.

(e) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Blood Glucose Levels/Glucose Tolerance Test:

Oral Glucose Tolerance: The (-/-) mice exhibited an impaired glucose tolerance when compared with that of their gender-matched (+/+) littermates and the historical mean.

These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose homeostasis, and therefore PRO1475 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

(f) *Bone Metabolism & Body Diagnostics*

(1) Tissue Mass & Lean Body Mass Measurements - DEXA

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

Obvious Observations: Obvious: The (-/-) mice were smaller than their (+/+) littermates and displayed clutched hind limbs when suspended by their tails.

Weight/Length:

The (-/-) mice exhibited decreased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean.

(2) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- 5 · DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

10 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

15 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

20 Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

30 Micro CT: micro CT: The male (-/-) mice exhibited decreased mean vertebral trabecular bone volume, number, thickness, and connectivity density when compared with their gender-matched (+/+) littermates and the historical means.

35 Mutant (-/-) mice deficient in the gene encoding PRO1475 polypeptides show a phenotype consistent with growth retardation and/or tissue wasting diseases as well as abnormal bone metabolism. These results are consistent with the observation of smaller appearance than their (+/+) littermates as well as decreased mean body weight and mean body length reported above. In addition, the mutant (-/-) mice exhibited decreased vertebral trabecular bone mineral content and density measurements suggestive of osteoporosis. Thus, antagonists or inhibitors of PRO1475 polypeptides or its encoding gene would mimic these abnormal metabolic related effects. On the other hand, PRO1475 polypeptides or agonists thereof would be useful in the prevention and/or treatment of such metabolic disorders as growth retardation, cachexia or other tissue wasting diseases as well as useful in

the treatment of bone disorders associated with bone loss.

66.30. Generation and Analysis of Mice Comprising DNA58732-1650 (UNQ750) Gene Disruptions

In these knockout experiments, the gene encoding PRO1481 polypeptides (designated as DNA58732-1650) (UNQ750) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_172979 Mus musculus RIKEN cDNA D730046L02 gene (D730046L02Rik); protein reference: Q8C6Z1 ACCESSION:Q8C6Z1 NID: Mus musculus (Mouse). Mucin 15 precursor; the human gene sequence reference: NM_145650 Homo sapiens mucin 15 (MUC15); the human protein sequence corresponds to reference: Q8N387 ACCESSION:Q8N387 NID: Homo sapiens (Human). MUC15 protein precursor.

The mouse gene of interest is RIKEN cDNA D730046L02 gene, ortholog of human MUC15 (mucin 15). Aliases include 4732460E09, PASIII, PAS3, GLYCOPROTEIN C, GLYCOPROTEIN 4, and COMPONENT II. MUC15 is a type I plasma membrane protein, consisting of a signal peptide, an extracellular, heavily glycosylated segment, a transmembrane segment, and short cytoplasmic C-terminus. A second isoform lacking the transmembrane segment may be secreted. The protein is expressed in a wide variety of tissues, including spleen, thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocyte, bone marrow, lymph node and lung. MUC15 likely plays a role in cell adhesion to extracellular matrix (Pallesen et al, Eur J Biochem 269(11):2755-63 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	19	39	23	81
Expected	20.25	40.5	20.25	81

Chi-Sq.= 2.06 Significance= 0.35700697 (hom/n)= 0.29 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_172979.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except liver, skeletal muscle, and bone.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.30.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA58732-1650 (UNQ750))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human mucin 15 (MUC15) resulted in the homozygous mutant mice exhibiting an enhanced sensorimotor gating/attention during prepulse inhibition testing when

compared with their wild-type littermates and the historical means. In addition, the mutant (-/-) mice exhibited immunological abnormalities. Gene disruption was confirmed by Southern blot.

(b) *Microarray Analysis*

Microarray analysis reveals overexpression of UNQ750 in breast tumors compared to normal breast tissue.

5 (c) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Prepulse inhibition of the acoustic startle reflex

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB + 120 dB - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

30 Results:

PPI: The (-/-) mice exhibited increased median prepulse inhibition during pp4, pp8, and pp12 when compared with the levels for their (+/+) littermates and the historical means, which is an indication of an enhanced sensorimotor gating/attention in the mutants.

(d) *Immunology Phenotypic Analysis*

35 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly

related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

(1) Fluorescence-activated cell-sorting (FACS) Analysis

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine

records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

5 Results:

Tissue Specific FACS-Project: The (-/-) mice exhibited an increased percentage of TCRB+ and a decreased percentage of B220+ cells in Peyer's patches when compared with those of the (+/+) mice. These results are indicative of an increase in activated T cells (TCRB+CD38+).

10 These results indicate that the knockout mice exhibited a decrease in a subset of B cells (pre-B cells, immature and mature B cells). Thus, the mutant homozygous mice exhibited immunological abnormalities associated with decreased levels of B cell progenitor cells. In addition, the knockout mice exhibit an increase in T cells.

15 These results show that knockout (-/-) mice exhibit immunological abnormalities compared to their wild-type (+/+) littermates. Antagonists (inhibitors) of PRO1481 polypeptides would be expected to mimic this phenotype. PRO1481 polypeptides or agonists thereof appear to act as a negative regulator of T cell production and a positive regulator of B cell development and would be useful in the development or maturation of B cells which could then participate in fast immune responses. Antagonists (inhibitors) of PRO1481 polypeptides would be useful in stimulating the production of T cells.

20 66.31. Generation and Analysis of Mice Comprising DNA68880-1676 (UNQ774) Gene Disruptions

In these knockout experiments, the gene encoding PRO1568 polypeptides (designated as DNA68880-1676) (UNQ774) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_173007 Mus musculus transmembrane 4 superfamily member 12 (Tm4sf12); protein reference: Q8BKT6 ACCESSION:Q8BKT6 NID: Mus musculus (Mouse). Mus musculus 9
25 days embryo whole body cDNA, RIKEN full-length enriched library, clone:D030012P12 product:TETRASPAN NET-2 homolog (Tm4sf12 protein); the human gene sequence reference: NM_012338 ACCESSION:NM_012338 NID:21264567 Homo sapiens Homo sapiens transmembrane 4 superfamily member tetraspan NET-2 (NET-2); the human protein sequence corresponds to reference: O95859 ACCESSION:O95859 NID: Homo sapiens (Human). TETRASPAN NET-2.

30 The mouse gene of interest is Tm4sf12 (transmembrane 4 superfamily member 12), ortholog of human TM4SF12. Aliases include 9030619E17, EST AI426782, NET-2, and tetraspan NET-2.

35 TM4SF12 is a putative integral plasma membrane protein and subunit of larger cell surface complexes that likely function in cell adhesion and signal transduction. TM4SF12 is a member of the tetraspanin superfamily, containing four transmembrane segments within a tetraspanin family domain. Although the physiological role of TM4SF12 is not known, tetraspanins are involved in adhesion-dependent signaling mediated by integrins, generally playing a role in processes such as cell adhesion, migration, fertilization, immunity, development, and metastasis (Serru et al, Biochim Biophys Acta 1478(1):159-63 (2000); Berditchevski, J Cell Sci 114(Pt 23):4143-51 (2001); Tarrant et al, Trends Immunol 24(11):610-7 (2003); Le Naour et al, Cancer Immunol Immunother 53(3):148-52

(2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	20	36	25	81
Expected	20.25	40.5	20.25	81

Chi-Sq.= 0.99 Significance= 0.6095709 (hom/n)= 0.26 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Coding exon 1 was targeted (NCBI accession NM_173007.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.31.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA68880-1676 (UNQ774))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human transmembrane 4 superfamily member 12 (TM4SF12) resulted in the homozygous mutant mice exhibited numerous ophthalmological abnormalities, including retinal microaneurysms and non-homogeneous retinal backgrounds. In addition, CAT-Scan analysis revealed moderate hydronephrosis in 2 of 3 homozygous mutants and 1 of 2 heterozygous mice analyzed. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Cardiovascular Phenotypic Analysis:*

In the area of cardiovascular biology, phenotypic testing was performed to identify potential targets for the treatment of cardiovascular, endothelial or angiogenic disorders. One such phenotypic test included optic fundus photography and angiography to determine the retinal arteriovenous ratio (A/V ratio) in order to flag various eye abnormalities. An abnormal A/V ratio signals such systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders. Such eye abnormalities may include but are not limited to the following: retinal abnormality is retinal dysplasia, various retinopathies, restenosis, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease,

Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct ophthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye.

Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). Many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions.

Results:

Fundus: The (-/-) mice exhibited unhealthy retinal beds with non-homogeneous backgrounds. Two (-/-) mice (M-79 and M-98) also exhibited white deposits above the retinal vessels that were approximately 2-3 times larger than the optic disc.

Angiogram: All 8 (-/-) mice exhibited multiple microaneurysms and leakage of the retinal capillaries bilaterally.

Such detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders such as retinal degeneration. Thus, antagonists of PRO1568 encoding genes would lead to similar pathological retinal changes, whereas agonists may be useful as therapeutic agents in the treatment of hypertension, atherosclerosis or other ophthalmological disorders including retinal degeneration and diseases associated with this condition (as indicated above).

Subsequent studies showed a sprouting angiogenesis defect in the UNQ774 knockout retina specifically in the nerve fiber layer (NFL); inner plexiform layer (IPL); and in the outer plexiform layer (OPL) (thus a three layered organization of the retinal vasculature showed a defective angiogenesis (sprouts) when compared with the wildtype (+/+) and heterozygous (+/-) sections [wholemount isolectin staining of the retina, 10x confocal images].

(c) Pathology/CAT Scan

CAT-Scan Protocol:

Mice were injected with a CT contrast agent, Omnipaque 300 (Nycomed Amershan, 300 mg of iodine per ml, 0.25ml per animal, or 2.50-3.75 g iodine/kg of body weight) intraperitoneally. After resting in the cage for ~ 10 minutes, the mouse was then sedated by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight). A CAT-scan was performed using a MicroCAT scanner (ImTek, Inc.) with the anesthetized animal lying prone on the test bed. Three dimensional images were reconstructed by the Feldkamp algorithm in a cluster of workstations using an ImTek 3D RECON software.

Results:

Among the 6 mice analyzed, 1 (+/-) mouse and 2 (-/-) mice exhibited moderate hydronephrosis.

66.32. Generation and Analysis of Mice Comprising DNA73735-1681 (UNQ779) Gene Disruptions

In these knockout experiments, the gene encoding PRO1573 polypeptides (designated as DNA73735-1681) (UNQ779) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_018778 Mus musculus claudin 8 (Cldn8); protein reference: Q9Z260 ACCESSION:Q9Z260 NID: Mus musculus (Mouse). Claudin-8; the human gene sequence reference: NM_199328 Homo sapiens claudin 8 (CLDN8); the human protein sequence corresponds to reference: P56748 ACCESSION:P56748 NID: Homo sapiens (Human). Claudin-8.

The mouse gene of interest is Cldn8 (claudin 8), ortholog of human CLDN8.

CLDN8 is an integral plasma membrane protein that functions as an adhesion molecule and component of tight junctions. The protein consists of a single claudin family domain (Pfam accession PF00822), which contains 4 transmembrane segments. CLDN8 is expressed primarily in lung and kidney and is particularly concentrated at the tight junctions along the aldosterone-sensitive nephron. CLDN8 is likely to play a role in paracellular cation transport and permeability (Yu et al, *J Biol Chem* 278(19):17350-9 (2003); Morita et al, *Proc Natl Acad Sci U S A* 96(2):511-6 (1999); Heiskala et al, *Traffic* 2(2):93-8 (2001); Li et al, *Am J Physiol Renal Physiol* 286(6):F1063-71 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	17	47	19	83
Expected	20.75	41.5	20.75	83

Chi-Sq.= 2.58 Significance= 0.2752708 (hom/n)= 0.21 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_018778.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except spleen, bone, heart, and adipose.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.32.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA73735-1681 (UNQ779))

5 (a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human claudin 8 (CLDN8) resulted in a decreased startle reflex in the mutant (-/-) mice. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: CNS/Neurology*

10 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

20 Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

25 *Prepulse inhibition of the acoustic startle reflex*

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB + 120 dB - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

Results:

PPI: The (-/-) mice exhibited a decreased startle response, suggesting a hearing impairment in the mutants.

35

66.33. Generation and Analysis of Mice Comprising DNA62845-1684 (UNQ782) Gene Disruptions

In these knockout experiments, the gene encoding PRO1599 polypeptides (designated as DNA62845-1684) (UNQ782) was disrupted. The gene specific information for these studies is as follows: the mutated mouse

gene corresponds to nucleotide reference: XM_196763 PREDICTED: Mus musculus RIKEN cDNA 2900092M14 gene (2900092M14Rik); protein reference: XP_196763 RIKEN cDNA 2900092M14 [Mus musculus]; the human gene sequence reference: NM_214710 Homo sapiens protease, serine-like 1 (PRSSL1); the human protein sequence corresponds to reference: Q6UWY2 ACCESSION: Q6UWY2 NID: Homo sapiens (Human). GLGL782.

5 The mouse gene of interest is Prssl1 (protease, serine-like 1), ortholog of human PRSSL1. Aliases include UNQ782, GLGL782, and 2900092M14Rik.

PRSSL1 is a putative secreted protease, consisting of a signal peptide and a trypsin-like serine protease domain (SMART accession SM00020).

10 Unfortunately, another mammalian locus (KLK10, kallikrein 10, GeneID: 5655) has also been referred to as PRSSL1 in the scientific literature and sequence databases. The disrupted locus described herein is not KLK10, and represents another gene altogether. No published information concerning PRSSL1 (the gene of interest for this project) could be found at the time of this writing--thus all refers to KLK10. Therefore, care is required in interpreting the scientific literature as database sequences.

15 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
20 Observed	23	33	24	80
Expected	20	40	20	80

Chi-Sq.= 1.1 Significance= 0.5769498 (hom/n)= 0.28 Avg. Litter Size= 10

Mutation Information

Mutation Type: Homologous Recombination (standard)

25 Description: Coding exons 2 and 3 were targeted (NCBI accession XM_196763.2).

1. Wild-type Expression Panel: Expression of the target gene was detected only in spinal cord, thymus, and spleen among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

30 66.33.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA62845-1684 (UNQ782))

(a) OVERALL PHENOTYPIC SUMMARY:

35 Mutation of the gene encoding the ortholog of human protease, serine-like 1 (PRSSL1) resulted in immunological abnormalities in (-/-) mice. The homozygous mutant mice exhibited decreased mean percentages of CD8 and NK cells and an increased mean percentage of B cells in the peripheral blood. In addition, the mutants exhibited increased mean serum TNF-alpha and MCP-1 responses to LPS challenge and an increased mean serum IgG2a response to ovalbumin challenge when compared with those of their wild-type littermates and the historical means. The knockout mice also showed inflammation of several tissues. In addition, the mutant (-/-) mice showed signs of obesity with increased mean total mass, percent total body fat, and total fat mass. Disruption of the target

gene was confirmed by Southern hybridization analysis.

(b) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

(1) *Flourescence-activated cell-sorting (FACS) Analysis*

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK

for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

FACS3: The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by decreased mean percentages of CD8 and NK cells and an increased mean percentage of B cells when compared with their (+/+) littermates and the historical means.

In summary, FACS analysis of immune cell composition indicates that knockout (-/-) mice exhibit immunological differences with respect to both B cells and cytotoxic T cells (CD8 - thymocyte subset which functions as a co-receptor for MHC class I molecules). Inhibitors or antagonists of PRO1599 would be useful in B cell production, whereas PRO1599 polypeptides would be expected to lead to the opposite effects. On the other hand, PRO1599 polypeptides appear to function as a positive regulator of CD8 and NK cells (the FACS results indicate that the homozygous mutant mice have a decreased mean percentage of both CD8 and natural killer cells). Natural killer cells are the first line of defense to viral infection since these cells have been implicated in viral immunity and in defense against tumors. Natural killer cells or NK cells act as effectors in antibody-dependent cell-mediated cytotoxicity and have been identified by their ability to kill certain lymphoid tumor cell lines *in vitro* without the need for prior immunization or activation. Thus, PRO1599 polypeptides or agonists thereof would be useful in the production of cytotoxic T cells and NK cells important for antibody dependent cell-mediated cytotoxicity.

(2) Acute Phase Response:

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sub-lethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNF α , MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

Acute Phase Response: The (-/-) mice exhibited increased mean serum TNF- α and MCP-1 responses to LPS challenge when compared with their gender-matched (+/+) littermates and the historical means.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO1599 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (TNF- α and

MCP-1 production) when challenged with the LPS endotoxin indicating a pro-inflammatory response. TNF-alpha and MCP-1 contribute to the later stages of B cell activation. This suggests that inhibitors or antagonists to PRO1599 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1599 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(3) *Ovalbumin Challenge*

Procedure: This assay was carried out on 7 wild types and 8 homozygotes. Chicken ovalbumin (OVA) is a T-cell dependent antigen, which is commonly used as a model protein for studying antigen-specific immune responses in mice. OVA is non-toxic and inert and therefore will not cause harm to the animals even if no immune response is induced. The murine immune response to OVA has been well characterized, to the extent that the immunodominant peptides for eliciting T cell responses have been identified. Anti-OVA antibodies are detectable 8 to 10 days after immunization using enzyme-linked immunosorbent assay (ELISA), and determination of different isotypes of antibodies gives further information on the complex processes that may lead to a deficient response in genetically engineered mice.

As noted above, this protocol assesses the ability of mice to raise an antigen-specific immune response. Animals were injected IP with 50 mg of chicken ovalbumin emulsified in Complete Freund's Adjuvant and 14 days later the serum titer of anti-ovalbumin antibodies (IgM, IgG1 and IgG2 subclasses) was measured. The amount of OVA-specific antibody in the serum sample is proportional to the Optical Density (OD) value generated by an instrument that scans a 96-well sample plate. Data was collected for a set of serial dilutions of each serum sample.

Results of this challenge:

Ovalbumin: The (-/-) mice exhibited an increased mean serum IgG2a response to ovalbumin challenge when compared with that of their (+/+) littermates and the historical mean.

In summary, the ovalbumin challenge studies indicate that knockout mice deficient in the gene encoding PRO1599 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response when challenged with the T-cell dependent OVA antigen. Thus, antagonists (inhibitors) of PRO1599 polypeptides would be useful for stimulating the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1599 polypeptides or agonists thereof, would be useful for inhibiting the immune response and thus would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases or autoimmune disease.

(c) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

5 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

10 DEXA: The female (-/-) mice exhibited increased mean total tissue mass, percent total body fat, and total fat mass when compared with their gender-matched (+/+) littermates and the historical means.

15 These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with obesity. Thus, PRO1599 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be important in the prevention and/or treatment of lipid storage diseases and/or obesity.

66.34. Generation and Analysis of Mice Comprising DNA71286-1687 (UNQ785) Gene Disruptions

20 In these knockout experiments, the gene encoding PRO1604 polypeptides (designated as DNA71286-1687) (UNQ785) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_008233 ACCESSION:NM_008233 NID:6680200 Mus musculus Mus musculus hepatoma-derived growth factor, related protein 2 (Hdgfrp2); protein reference: O35540 O35540 O35540 HEPATOMA-DERIVED GROWTHFACTOR; the human gene sequence reference: NM_032631 Homo sapiens hepatoma-derived growth factor-related protein 2 (HDGF2), transcript variant 2; the human protein sequence corresponds to reference: Q9BW08 ACCESSION:Q9BW08 NID: Homo sapiens (Human). Similar to hepatoma-derived growth factor, related protein 2.

25 The mouse gene of interest is Hdgfrp2 (hepatoma-derived growth factor, related protein 2), ortholog of human HDGF2. Aliases include MGC2641, hepatoma-derived growth factor 2, and HRP-2.

30 HDGF2 is a putative nuclear protein expressed primarily in testis and skeletal muscle. The protein contains a PWWP domain and a bipartite nuclear localization signal. PWWP domains are typically found in nuclear proteins and are likely involved in protein-protein interactions. HDGF2 is structurally similar to hepatoma-derived growth factor (HDGF), a nuclear protein that stimulates DNA synthesis and cell proliferation when over-expressed in cell lines or when applied exogenously to cells. The apparent mitogenic activity of HDGF is dependent on its ability to enter the nucleus (Izumoto et al, Biochem Biophys Res Commun 238(1):26-32 (1997); Kishima et al, J Biol Chem 277(12):10315-22 (2002)).

35 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for

example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	20	36	17	73
5 Expected	18.25	36.5	18.25	73

Chi-Sq.= 7.54 Significance= 0.023052063 (hom/n)= 0.18 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 3 were targeted (NCBI accession NM_008233.1).

- 10 1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.34.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA71286-1687 (UNQ785))

15 (a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human hepatoma-derived growth factor, related protein 2 (HDGF2) resulted in the homozygous mutant mice exhibiting increased mean serum alkaline phosphatase levels when compared with that of their wild-type littermates and the historical means. During circadian testing, the mutant (-/-) mice exhibited hyperactivity during all light and dark periods. In addition, the female mutants exhibited a decreased mean skin fibroblast proliferation rate. Male (-/-) mice exhibited decreased bone mineral content and density measurements. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Phenotypic Analysis: Metabolism -Blood Chemistry*

In the area of metabolism, targets may be identified for the treatment of metabolic disorders. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In addition to measuring blood glucose levels the following blood chemistry tests are also routinely performed: Alkaline Phosphatase; Alanine Amino-Transferase; Albumin; Bilirubin; Phosphorous; Creatinine; BUN = Blood Urea Nitrogen; Calcium; Uric Acid; Sodium; Potassium; and Chloride.

30 Results:

Both the male and female (-/-) mice exhibited increased mean serum alkaline phosphatase levels when compared with that of their gender-matched (+/+) littermates and the historical means. This result is most likely due to changes in the liver.

(c) *Phenotypic Analysis: CNS/Neurology*

35 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not

limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Circadian Test Description:

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

The female (-/-) mice exhibited increased ambulatory counts (hyperactivity) during the 12-hour habituation and all light and dark periods of home-cage activity testing when compared with their gender-matched (+/+) littermates and the historical mean. These results demonstrate an enhanced circadian rhythm. Home-cage activity testing is also suggestive of increased activity or hyperactivity which is consistent with generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, and sensory disorders.

(d) Adult skin cell proliferation:

Procedure: Skin cells were isolated from 16 week old animals (2 wild type and 4 homozygotes). These were developed into primary fibroblast cultures and the fibroblast proliferation rates were measured in a strictly controlled protocol. The ability of this assay to detect hyper-proliferative and hypo-proliferative phenotypes has been demonstrated with p53 and Ku80. Proliferation was measured using Brdu incorporation.

Specifically, in these studies the skin fibroblast proliferation assay was used. An increase in the number of cells in a standardized culture was used as a measure of relative proliferative capacity. Primary fibroblasts were established from skin biopsies taken from wild type and mutant mice. Duplicate or triplicate cultures of 0.05 million cells were plated and allowed to grow for six days. At the end of the culture period, the number of cells present in the culture was determined using a electronic particle counter.

Results:

The female (-/-) mice exhibited a decreased mean skin fibroblast proliferation rate when compared with

their gender-matched (+/+) littermates.

Thus, homozygous mutant mice demonstrated a hypo-proliferative phenotype. As suggested by these observations, antagonists or inhibitors of PRO1604 polypeptides would mimic this hypo-proliferative phenotype and could function as tumor suppressors and would be useful in decreasing abnormal cell proliferation.

(e) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male (-/-) mice seemed to show a trend for decreased bone mineral content and vertebrae bone mineral density as well as total body and femur bone mineral density when compared with the values for their gender-matched (+/+) littermates and the historical means.

MicroCT: The male knockouts seemed to show a trend for decreased trabecular thickness and connectivity density as well as midshaft femur total area when compared with that of their gender-matched (+/+) littermates and the historical mean. Both the DEXA and MicroCT results are barely 1 SD below the median.

66.35. Generation and Analysis of Mice Comprising DNA77648-1688 (UNO786) Gene Disruptions

In these knockout experiments, the gene encoding PRO1605 polypeptides (designated as DNA77648-

1688) (UNQ786) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_175098 Mus musculus RIKEN cDNA 6330407D12 gene (6330407D12Rik); protein reference: Q8BIS8 ACCESSION:Q8BIS8 NID: Mus musculus (Mouse). Mus musculus adult male medulla oblongata cDNA, RIKEN full-length enriched library, clone:6330407D12 product: weakly similar to N- ACETYLGLUCOSAMINYLTRANSFERASE; the human gene sequence reference: NM_138771
 5 ACCESSION:NM_138771 NID: gi 20270308 ref NM_138771.1 Homo sapiens alpha-1,3(6)-mannosylglycoprotein beta-1,6-N-acetyl-glucosaminyltransferase-like (LOC90693); the human protein sequence corresponds to reference: Q96EE4 ACCESSION:Q96EE4 NID: Homo sapiens (Human). Hypothetical protein.

10 The mouse gene of interest is RIKEN cDNA 6330407D12 gene, ortholog of human alpha-1,3(6)-mannosylglycoprotein beta-1,6-N-acetyl-glucosaminyltransferase-like. Aliases include EST AA675040.

The hypothetical protein of 140 amino acids, which consists of a signal peptide and no other conserved domain, is predicted to be located in the Golgi apparatus or in the extracellular space (secreted). The protein is structurally related to N-terminal segments of MGAT5 (mannosyl [alpha-1,6-]-glycoprotein
 15 beta-1,6-N-acetyl-glucosaminyltransferase) and MGAT5B (mannosyl [alpha-1,6-]-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase, isoenzyme B), glycosyltransferases of approximately 750 amino acids that catalyze glycoprotein oligosaccharide biosynthesis. MGAT5 is located in the membrane of the Golgi apparatus and is also secreted. Secreted MGAT5 is likely to release fibroblast growth factor from heparan sulfate proteoglycans by a mechanism independent of glycosylation, enabling FGF-2 to activate its receptor on target cells
 20 (Saito et al, *J Biol Chem* 277(19):17002-8 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}
 25 /C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	14	50	26	90
Expected	22.5	45	22.5	90

30 Chi-Sq.= 1.3 Significance= 0.5220458 (hom/n)= 0.27 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: The first coding exon was targeted (NM_175098.2).

- 35 1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.35.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA77648-1688 (UNQ786))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human alpha-1,3(6)-mannosylglycoprotein beta-1,6-N-acetyl-glucosaminyl transferase-like resulted in the mutant (-/-) mice exhibiting increased triglyceride levels. Four of the (-/-) mice exhibited an increased intra-cytoplasmic vacuolization of glycogen in hepatocytes.

5 Gene disruption was confirmed by Southern blot.

(b) *Pathology*

Microscopic: Among the 6 (-/-) mice analyzed, 4 exhibited moderately increased intra-cytoplasmic vacuolization of glycogen in hepatocytes.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

10 (c) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum triglycerides.

15 *Blood Lipids*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The male (-/-) mice exhibited increased mean serum triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means.

25 As summarized above, the (-/-) mice exhibited increased mean serum triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO1605 gene can serve as a model for cardiovascular disease. PRO1605 polypeptides or its encoding gene would be useful in regulating blood lipids such as triglycerides. Thus, PRO1605 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, hypertriglyceridemia, diabetes and/or obesity.

30

66.36. Generation and Analysis of Mice Comprising DNA77301-1708 (UNQ803) Gene Disruptions

In these knockout experiments, the gene encoding PRO1693 polypeptides (designated as DNA77301-1708) (UNQ803) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_178678 Mus musculus leucine rich repeat transmembrane neuronal 3 (Lrrtm3); protein reference: Q8BGJ7 ACCESSION: Q8BGJ7 NID: Mus musculus (Mouse). Mus musculus 16 days neonate cerebellum cDNA, RIKEN full-length enriched library, clone:9630003D05 product: hypothetical Leucine-rich repeat, typical subtype containing protein, full insert sequence; the human gene sequence reference:

35

NM_178011 Homo sapiens leucine rich repeat transmembrane neuronal 3 (LRRTM3); the human protein sequence corresponds to reference: Q86VH5 ACCESSION:Q86VH5 NID: Homo sapiens (Human). Leucine-rich repeat transmembrane neuronal 3 protein (GFNV803).

The mouse gene of interest is *Lrrtm3* (leucine rich repeat transmembrane neuronal 3), ortholog of human LRRTM3. Aliases include 9630044H04Rik and leucine-rich repeat transmembrane neuronal 3 protein.

5 LRRTM3 is a putative integral plasma membrane protein, consisting of a signal peptide, several leucine-rich repeats, a transmembrane segment, and a potential cytoplasmic C-terminal domain. The protein is expressed primarily in the nervous system of vertebrates. LRRTM3 may function as a cell adhesion molecule or signal-transducing receptor, possibly playing a role in development and maintenance of the nervous system (Lauren et al, *Genomics* 81(4):411-21 (2003)).

10 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	24	25	15	64
Expected	16	32	16	64

Chi-Sq.= 0.15 Significance= 0.9277435 (hom/n)= 0.25 Avg. Litter Size= 9

20 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 2 was targeted (NCBI accession NM_178678.2).

1. Wild-type Expression Panel: Expression of the target gene was detected only in brain, spinal cord, and eye among the 13 adult tissue samples tested by RT-PCR.

25 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.36.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA77301-1708 (UNO803))

(a) *OVERALL PHENOTYPIC SUMMARY:*

30 Mutation of the gene encoding the ortholog of human leucine rich repeat transmembrane neuronal 3 (LRRTM3) resulted in the homozygous mutant mice exhibiting an increased mean absolute neutrophil count when compared with the levels for their wild-type littermates and the historical means. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

35 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a

reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

5 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate
10 extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination
15 of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the
20 area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune
25 response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

Hematology Analysis:

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology
30 analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

Results:

Hematology: The (-/-) mice exhibited an increased mean absolute neutrophil count when compared with that of their (+/+) littermates and the historical mean.

35 These results indicate that mutant (-/-) mice exhibit immunological abnormalities compared with their wildtype littermates. In summary, the hematology results indicate that the homozygous mutant mice exhibited increased neutrophils indicating elevated levels of precursors of macrophages with increased phagocytic activity or ability to engulf or kill extracellular pathogens.

66.37. Generation and Analysis of Mice Comprising DNA68883-1691 (UNQ826) Gene Disruptions

In these knockout experiments, the gene encoding PRO1753 polypeptides (designated as DNA68883-1691) (UNQ826) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_010959 Mus musculus oncoprotein induced transcript 3 (Oit3); protein reference: Q8C9U1 ACCESSION:Q8C9U1 NID: Mus musculus (Mouse). Mus musculus 0 day neonate thymus cDNA, RIKEN full-length enriched library, clone:A430107A04 product:ALC homolog; the human gene sequence reference: NM_152635 Homo sapiens oncoprotein induced transcript 3 (OIT3); the human protein sequence corresponds to reference: Q8WWZ8 ACCESSION:Q8WWZ8 NID: Homo sapiens (Human). LZP (Hypothetical protein FLJ39116) (PPFL826).

The mouse gene of interest is Oit3 (oncoprotein induced transcript 3), ortholog of human OIT3. Aliases include LZP, EF-9, FLJ39116, and liver-specific ZP domain-containing protein.

OIT3 is a putative secreted protein expressed primarily in liver. The protein contains a signal peptide, three tandem epidermal growth factor-like domains, and a novel zona pellucida domain. Although a truncated form of the protein can be detected in blood, OIT3 is located mainly on the nuclear envelope of hepatocytes. OIT3 gene is activated by oncoprotein E2a-Pbx1 in NIH 3T3 fibroblasts but is rarely expressed in hepatocellular carcinoma, suggesting that OIT3 may be a useful negative marker for hepatocellular carcinoma. The biological role of OIT3 is not known (Fu and Kamp, *Mol Cell Biol* 17(3):1503-12 (1997); Xu et al, *Hepatology* 38(3):735-44 (2003); Xu et al, *DNA Seq* 15(2):81-7 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	19	41	15	75
Expected	18.75	37.5	18.75	75

Chi-Sq.= 5.82 Significance= 0.054475725 (hom/n)= 0.2 Avg. Litter Size= 10

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_010959.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.37.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA68883-1691 (UNQ826))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human oncoprotein induced transcript 3 (OIT3) resulted in the male homozygous mutant mice exhibiting an increased anxiety-like response during open field testing when

compared with their gender-matched wild-type littermates and the historical mean. In addition, tissue specific FACS revealed an immunological alteration in the mutant (-/-) mice marked by decreased percentage of B220hiCD43-, IgM+, and IgD+. Female (-/-) mice exhibited decreased bone mineral content and bone mineral density measurements. UNQ826 shows high expression in both normal and diseased liver tissue. Disruption of the target gene was confirmed by Southern hybridization analysis.

5

(b) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

10

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

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T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

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In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

25

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

30

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

35

The following test was performed:

*Flourescence-activated cell-sorting (FACS) Analysis/Tissue Specific FACS*Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

Tissue Specific FACS-Project: The (-/-) mice exhibited a decreased percentage of B220hiCD43-, IgM+, and IgD+ cells in bone marrow when compared with that of their (+/+) littermates. These results are indicative of a decrease in the bone marrow of a subset of pre-B, immature and mature B cells. Thus, PRO1753 polypeptides are important in the development of B cell population in the bone marrow and would be useful in stimulating B cell production.

(c) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Open field test:

Several targets of known drugs have exhibited phenotypes in the open field test. These include knockouts

of the serotonin transporter, the dopamine transporter (Giros et al., Nature. 1996 Feb 15;379(6566):606-12), and the GABA receptor (Homanics et al., Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):4143-8). An automated open-field assay was customized to address changes related to affective state and exploratory patterns related to learning. First, the field (40 X 40 cm) was selected to be relatively large for a mouse, thus designed to pick up changes in locomotor activity associated with exploration. In addition, there were 4 holes in the floor to allow for nose-poking, an activity specifically related to exploration. Several factors were also designed to heighten the affective state associated with this test. The open-field test is the first experimental procedure in which the mice are tested, and the measurements that were taken were the subjects' first experience with the chamber. In addition, the open-field was brightly lit. All these factors will heighten the natural anxiety associated with novel and open spaces. The pattern and extent of exploratory activity, and especially the center-to-total distance traveled ratio, may then be able to discern changes related to susceptibility to anxiety or depression. A large arena (40 cm x 40 cm, VersaMax animal activity monitoring system from AccuScan Instruments) with infrared beams at three different levels was used to record rearing, hole poke, and locomotor activity. The animal was placed in the center and its activity was measured for 20 minutes. Data from this test was analyzed in five, 4-minute intervals. The total distance traveled (cm), vertical movement number (rearing), number of hole pokes, and the center to total distance ratio were recorded.

The propensity for mice to exhibit normal habituation responses to a novel environment is assessed by determining the overall change in their horizontal locomotor activity across the 5 time intervals. This calculated slope of the change in activity over time is determined using normalized, rather than absolute, total distance traveled. The slope is determined from the regression line through the normalized activity at each of the 5 time intervals. Normal habituation is represented by a negative slope value.

Results:

Openfield2: The male (-/-) mice exhibited decreased median sum time-in-center when compared with their gender-matched (+/+) littermates and the historical mean, suggesting an increased anxiety-like response in the mutants. In addition, whiskers were absent in 2 of 8 (+/+) wild-type mice and 6 of 8 (-/-) knockout mice. Knockout mice with absent whiskers at increased frequency is probably related to the anxiety phenotype.

In summary, the open field testing revealed a phenotype associated with increased anxiety which could be associated with mild to moderate anxiety, anxiety due to a general medical condition, and/or bipolar disorders; hyperactivity; sensory disorders; obsessive-compulsive disorders, schizophrenia or a paranoid personality. Thus, PRO1753 polypeptides or agonists thereof would be useful in the treatment of such neurological disorders.

(d) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized

animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

DEXA:

The female (-/-) mice exhibited decreased mean bone mineral content and bone mineral density in total body and vertebrae when compared with their gender-matched (+/+) littermates and the historical means.

Thus, mutant (-/-) mice deficient in the gene encoding PRO1753 polypeptides show a phenotype consistent with osteoporosis marked by decreased bone mineral content and density measurements. Thus, antagonists or inhibitors of PRO1753 polypeptides or its encoding gene would mimic these abnormal metabolic related effects. On the other hand, PRO1753 polypeptides or agonists thereof would be useful in the prevention and/or treatment of bone disorders associated with bone loss.

66.38. Generation and Analysis of Mice Comprising DNA76396-1698 (UNQ828) Gene Disruptions

In these knockout experiments, the gene encoding PRO1755 polypeptides (designated as DNA76396-1698) (UNQ828) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_175696 Mus musculus RIKEN cDNA C530028O21 gene (C530028O21Rik); protein reference: Q6P1B3 ACCESSION:Q6P1B3 NID: Mus musculus (Mouse). C530028O21Rik protein; the human gene sequence reference: NM_153685 Homo sapiens hypothetical protein DKFZp547D2210 (DKFZp547D2210); the human protein sequence corresponds to reference: Q8IYJ0 ACCESSION:Q8IYJ0 NID: Homo sapiens (Human). Hypothetical protein DKFZp547D2210.

The mouse gene of interest is RIKEN cDNA C530028O21 gene, ortholog of human hypothetical protein DKFZp547D2210. Aliases include EST A1255183 and DKFZp547D2210.

Hypothetical protein DKFZp547D2210 is a likely type I integral membrane protein, consisting of a signal peptide and a transmembrane domain. The function of this protein is not known, and its predicted cell location is ambiguous.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	33	16	65
Expected	16.25	32.5	16.25	65

Chi-Sq.= 0.09 Significance= 0.95599747 (hom/n)= 0.26 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 4 were targeted (NCBI accession NM_175696.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.38.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA76396-1698 (UNQ828))

(a) *OVERALL PHENOTYPIC SUMMARY:*

- 1.0 Mutation of the gene encoding the ortholog of a human hypothetical membrane protein resulted in an the female homozygous mutant mice exhibiting an increased mean skin fibroblast proliferation rate when compared with that of their gender-matched wild-type littermates and the historical mean. In addition, the male (-/-) mice showed an impaired glucose tolerance. The (-/-) mice also exhibited decreased mean serum IgG1 levels. UNQ828 is highly expressed in the CNS compared to other normal tissues. The endothelium also shows moderately high expression. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

- 2.0 In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

- 2.5 Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Blood Glucose Levels/Glucose Tolerance Test:

- 3.0 Oral Glucose Tolerance: The male (-/-) mice exhibited a modestly impaired glucose tolerance when compared with that of their gender-matched (+/+) littermates and the historical mean.

- 3.5 These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose homeostasis, and therefor PRO1755 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

(c) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly
 5 related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental
 10 process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health
 15 threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating
 20 cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated
 25 inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune
 30 response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

35 The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

Serum Imm. 2: The (-/-) mice exhibited a decreased mean serum IgG1 level when compared with that of their (+/+) littermates, the (+/+) mice for the project run, and the historical median.

Thus, mutant (-/-) mice showed decreased IgG1 serum immunoglobulins compared to their gender-matched (+/+) littermates. These immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. The observed phenotype suggests that the PRO1755 polypeptide is a regulator of inflammatory responses. Thus, the gene encoding PRO1755 polypeptides is essential for making IgG1 immunoglobulins (or gamma globulins). These immunological abnormalities suggest that PRO1755 polypeptides may be important agents which could stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, antagonists (inhibitors) of PRO1755 polypeptides can play a role in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(d) Adult skin cell proliferation:

Procedure: Skin cells were isolated from 16 week old animals (2 wild type and 4 homozygotes). These were developed into primary fibroblast cultures and the fibroblast proliferation rates were measured in a strictly controlled protocol. The ability of this assay to detect hyper-proliferative and hypo-proliferative phenotypes has been demonstrated with p53 and Ku80. Proliferation was measured using Brdu incorporation.

Specifically, in these studies the skin fibroblast proliferation assay was used. An increase in the number of cells in a standardized culture was used as a measure of relative proliferative capacity. Primary fibroblasts were established from skin biopsies taken from wild type and mutant mice. Duplicate or triplicate cultures of 0.05 million cells were plated and allowed to grow for six days. At the end of the culture period, the number of cells present in the culture was determined using a electronic particle counter.

Results:

Skin Proliferation: The female (-/-) mice exhibited an increased mean skin fibroblast proliferation rate when compared with that of their gender-matched (+/+) littermates and the historical mean. Two out of the four (-/-) mice showed significantly increased proliferation.

Thus, homozygous mutant mice demonstrated a hyper-proliferative phenotype. As suggested by these observations, PRO1755 polypeptides or agonists thereof could function as tumor suppressors and would be useful in decreasing abnormal cell proliferation.

66.39. Generation and Analysis of Mice Comprising DNA71235-1706 (UNQ839) Gene Disruptions

In these knockout experiments, the gene encoding PRO1777 polypeptides (designated as DNA71235-1706) (UNQ839) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_028710 Mus musculus RIKEN cDNA 6330406P08 gene (6330406P08Rik); protein reference: Q9D3B4 ACCESSION:Q9D3B4 NID: Mus musculus (Mouse). 6330406P08RIK PROTEIN; the human gene sequence reference: NM_014960 Homo sapiens Arylsulfatase G (KIAA1001); the human protein sequence corresponds to reference: Q96EG1 ACCESSION:Q96EG1 NID: Homo sapiens (Human). Arylsulfatase G.

The mouse gene of interest is RIKEN cDNA 6330406P08 gene, ortholog of human ARSG (Arylsulfatase G). Aliases include KIAA1001.

ARSG is an enzyme that likely catalyzes the hydrolysis of arylsulfoester bonds. The location of this enzyme is not clearly known. Bioinformatic analyses of ARSG suggest that the enzyme may be located in lysosomes or may be secreted. ARSG expressed in COS7 cells is located in the endoplasmic reticulum (Ferrante et al, *Eur J Hum Genet* 10(12):813-8 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	12	33	12	57
Expected	14.25	28.5	14.25	57

Chi-Sq.= 0.01 Significance= 0.99501246 (hom/n)= 0.25 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_028710.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle, bone, and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.39.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA71235-1706 (UNQ839))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human Arylsulfatase G (ARSG) resulted in immunological abnormalities in (-/-) mice. The homozygous mutant mice exhibited a decreased mean percentage of natural killer cells in the peripheral blood and an increased mean serum IgG3 level when compared with the levels for their wild-type littermates and the historical means. The female mutants also exhibited a decreased mean skin fibroblast proliferation rate. The male (-/-) mice also exhibited an increased mean percent total body fat mass and decreased mean bone mineral density-related measurements. Micro-CT results showed a decreased mean femoral mid-shaft cross-sectional area. The female (-/-) mice exhibited an increased median ambulatory counts during home cage testing indicating an enhanced circadian rhythm. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Microarray Analysis*

Microarray analysis shows UNQ839 being highly overexpressed in breast tumors compared to normal breast tissue.

(c) *Inmunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often

multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

5 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

10 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also
15 secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

20 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

25 In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and
30 thus ameliorate immune related disease.

The following tests were performed:

(1) *Flourescence-activated cell-sorting (FACS) Analysis*

Procedure:

35 FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and

lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

5 The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

10 FACS: The (-/-) mice exhibited an altered distribution of different leukocyte subsets, characterized by a decreased mean percentage of natural killer cells in the peripheral blood when compared with their wild-type littermates and the historical mean.

In summary, the FACS results indicate that the homozygous mutant mice have an impaired immune system, especially in view of the decreased mean percentage of natural killer cells which is an indicator of a negative phenotype associated with knocking out the DNA71235-1706 gene which encodes PRO1777 polypeptides. Natural killer cells are the first line of defense to viral infection since these cells have been implicated in viral immunity and in defense against tumors. Natural killer cells or NK cells act as effectors in antibody-dependent cell-mediated cytotoxicity and have been identified by their ability to kill certain lymphoid tumor cell lines *in vitro* without the need for prior immunization or activation. However, their known function in host defense is in the early phases of infection with several intracellular pathogens, particularly herpes viruses. Thus, PRO1777 polypeptides and agonists thereof would be important for a healthy immune system and would be useful in stimulating the immune system particularly during viral infections.

(2) Serum Immunoglobulin Isotyping Assay:

25 The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

30 Serum Imm. 2: The (-/-) mice exhibited an increased mean serum IgG3 level when compared with that of their (+/+) littermates, the (+/+) mice for the project run, and the historical median.

The serum immunoglobulin isotyping assay revealed that homozygous adults exhibited increased serum IgG3 levels. Thus, homozygotes showed elevated serum immunoglobulins compared with the (+/+) littermates. IgG3 immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. These immunological abnormalities suggest that antagonists or inhibitors of PRO1777 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1777 polypeptides or agonists thereof would inhibit the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(d) Adult skin cell proliferation:

Procedure: Skin cells were isolated from 16 week old animals (2 wild type and 4 homozygotes). These were developed into primary fibroblast cultures and the fibroblast proliferation rates were measured in a strictly controlled protocol. The ability of this assay to detect hyper-proliferative and hypo-proliferative phenotypes has been demonstrated with p53 and Ku80. Proliferation was measured using Brdu incorporation.

5 Specifically, in these studies the skin fibroblast proliferation assay was used. An increase in the number of cells in a standardized culture was used as a measure of relative proliferative capacity. Primary fibroblasts were established from skin biopsies taken from wild type and mutant mice. Duplicate or triplicate cultures of 0.05 million cells were plated and allowed to grow for six days. At the end of the culture period, the number of cells present in the culture was determined using a electronic particle counter.

10 Results:

Skin Proliferation: The female (-/-) mice exhibited a decreased mean skin fibroblast proliferation rate when compared with that of their gender-matched (+/+) littermates and the historical mean.

Thus, homozygous mutant mice demonstrated a hypo-proliferative phenotype. As suggested by these observations, antagonists or inhibitors of PRO1777 polypeptides would mimic this hypo-proliferative phenotype and could function as tumor suppressors and would be useful in decreasing abnormal cell proliferation. These results are consistent with the microarray data showing overexpression of this gene in breast tumors.

15

(e) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

20

25

30 Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Circadian Test Description:

35 Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour

intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The female (-/-) mice exhibited a notably increased median ambulatory counts during both dark periods when compared with the number for their gender-matched (+/+) littermates and the historical means.

These results demonstrate an enhanced circadian rhythm. Home-cage activity testing is also suggestive of increased activity or hyperactivity which is consistent with generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, and sensory disorders.

(f) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImusTM Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male (-/-) mice exhibited decreased mean bone mineral density-related measurements with decreased bone mineral content and mean bone mineral density when compared with those of their gender-matched (+/+) littermates and the historical means.

Micro CT: The male (-/-) mice also exhibited decreased mean femoral mid-shaft cross-sectional area when

compared with that of their gender-matched (+/+) littermates and the historical mean.

These results demonstrate that knockout mutant mice exhibit abnormal bone metabolism with decreased bone measurements similar to osteoporosis characterized by decrease in bone mass with decreased density and possibly fragility leading to bone fractures. Thus, it appears that PRO1777 polypeptides or agonists thereof would be useful in maintaining bone homeostasis. In addition, PRO1777 polypeptides or its encoding gene would be useful in bone healing or for the treatment of arthritis or osteoporosis; whereas antagonists to PRO1777 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including arthritis, osteoporosis, and osteopenia.

The male (-/-) mice also exhibited increased mean percent total body fat and total fat mass when compared with their gender-matched (+/+) littermates and the historical means.

These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with obesity. Pathological observations are consistent with the radiological findings. Thus, PRO1777 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be important in the prevention and/or treatment of lipid storage diseases and/or obesity.

66.40. Generation and Analysis of Mice Comprising DNA77652-2505 (UNQ850) Gene Disruptions

In these knockout experiments, the gene encoding PRO1788 polypeptides (designated as DNA77652-2505) (UNQ850) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: XM_485965 PREDICTED: Mus musculus RIKEN cDNA 9530051K01 gene (9530051K01Rik); protein reference: XP_485965 similar to hypothetical protein, estradiol-induced [Mus musculus]; the human gene sequence reference: NM_015516 Homo sapiens hypothetical protein, estradiol-induced (E2IG4); the human protein sequence corresponds to reference: Q9UJX9 ACCESSION:Q9UJX9 NID: Homo sapiens (Human). E2IG4.

The mouse gene of interest is RIKEN cDNA 9530051K01 gene, ortholog of human TSK (likely ortholog of chicken tsukushi). Aliases include E2IG4.

TSK is a secreted protein, consisting of a signal peptide, a leucine-rich repeat N-terminal domain, and several leucine-rich repeats. TSK binds with bone morphogenic protein or chordin to form a ternary complex and inhibits BMP-induced Hensen's node formation during gastrulation. TSK likely plays a role in dorsalization during embryonic development (Ohta et al, Dev Cell 7(3):347-58 (2004)). TSK is also expressed in estrogen-responsive breast cancer cells and is proposed to play a role in breast tissue remodeling or epithelium-stroma interactions (Charpaentier et al, Cancer Res 60(21):5977-83 (2000)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	42	26	89
Expected	22.25	44.5	22.25	89

Chi-Sq.= 0.78 Significance= 0.6770569 (hom/n)= 0.27 Avg. Litter Size= 10

Mutation Information

5 Mutation Type: Homologous Recombination (standard)

Coding exon 2 was targeted (NCBI accession AK035461.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in spleen; liver; skeletal muscle; stomach, small intestine, and colon; heart; and adipose among the 13 adult tissue samples tested by RT-PCR.

10 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.40.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA77652-2505 (UNO850))

(a) *OVERALL PHENOTYPIC SUMMARY:*

15 Mutation of the gene encoding the ortholog of human likely ortholog of chicken tsukushi (TSK) resulted in the mutant (-/-) mice exhibiting increased mean serum IgM levels. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

20 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

25 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

30 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic

35 T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

5 In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

10 The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

Serum Imm. 2: The (-/-) mice exhibited an increased mean serum IgM level when compared with that of their (+/+) littermates, the (+/+) mice for the project run, and the historical median.

20 Mutant (-/-) mice exhibited elevation of IgM serum immunoglobulins compared to their gender-matched (+/+) littermates. IgM immunoglobulins are the first to be produced in a humoral immune response for neutralization of bacterial toxins and are particularly important in activating the complement system. The observed phenotype suggests that the PRO1788 polypeptide is a negative regulator of inflammatory responses. These immunological abnormalities suggest that inhibitors (antagonists) of PRO1788 polypeptides would be important agents which could stimulate the immune system (such as T cell proliferation) and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO1788 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

30 66.41. Generation and Analysis of Mice Comprising DNA45409-2511 (UNQ855) Gene Disruptions

In these knockout experiments, the gene encoding PRO1864 polypeptides (designated as DNA45409-2511) (UNQ855) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_024270 Mus musculus STARD3 N-terminal like (Stard3nl); protein reference: Q9DCI3 ACCESSION:Q9DCI3 NID: Mus musculus (Mouse). MLN64 N-terminal domain homolog (STARD3 N-terminal like protein); the human gene sequence reference: NM_032016 Homo sapiens STARD3 N-terminal like (STARD3NL); the human protein sequence corresponds to reference: O95772 ACCESSION:O95772 NID: Homo sapiens (Human). H_NH1021A08.1 PROTEIN (UNKNOWN) (PROTEIN

FOR MGC:14607) (SIMILAR TO STEROIDOGENIC ACUTE REGULATORY PROTEIN RELATED).

The mouse gene of interest is Stard3nl (STARD3 N-terminal like), ortholog of human STARD3NL. Aliases include MENTHO, 0610035N01Rik, 6530409L22Rik, MGC3251, and MLN64 N-terminal domain homolog. STARD3NL is a ubiquitously expressed integral membrane protein located primarily on late endosomes. Bioinformatic analyses suggest that STARD3NL may also be an extracellular protein. STARD3NL consists of four transmembrane segments within a MENTAL (MLN64 N-terminal) domain, which is involved in targeting and anchoring proteins to late endosomes. STARD3NL is likely to play a role in endosomal transport (Alpy et al, *JBiol Chem* 277(52):50780-7 (2002); Clark et al, *Genome Res* 13(10):2265-70 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	15	35	24	74
Expected	18.5	37	18.5	74

Chi-Sq.= 2.82 Significance= 0.24414329 (hom/n)= 0.3 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_024270.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.41.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA45409-2511 (UNQ855))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human STARD3 N-terminal like (STARD3NL) resulted in the mutant (-/-) mice exhibiting hydronephrosis. Whiskers were absent in 4 of 8 (+/+) mice and 5 of 8 (-/-) mice; defecation was absent in 4 of 8 (+/+) mice and 5 of 8 (-/-) mice. Blood chemistry results showed abnormal levels of urobilinogen, nitrites, protein and ketone bodies in (+/+), (+/-) and (-/-) mice. Gene disruption was confirmed by Southern blot.

(b) CAT-Scan Protocol:

Mice were injected with a CT contrast agent, Omnipaque 300 (Nycomed Amershan, 300 mg of iodine per ml, 0.25ml per animal, or 2.50-3.75 g iodine/kg of body weight) intraperitoneally. After resting in the cage for ~ 10 minutes, the mouse was then sedated by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight). A CAT-scan was performed using a MicroCAT scanner (ImTek, Inc.) with the anesthetized animal lying prone on the test bed. Three dimensional images were reconstructed by the Feldkamp algorithm in a cluster of workstations using an ImTek 3D RECON software.

Results:

Of the three (-/-) mice examined, two (-/-) [M-226 and F-180] exhibited hydronephrosis. Hydronephrosis is a condition wherein there is cystic distension of the kidney caused by an accumulation of urine in the kidney pelvis as a result of obstruction to outflow and is accompanied by atrophy of the kidney structure and cyst formation. Therefore, deletion of the gene encoding PRO1864 polypeptides causes atrophy of the kidneys and cyst formation.

(c) Phenotypic Analysis: Metabolism -Blood Chemistry

In the area of metabolism, targets may be identified for the treatment of diabetes or other metabolic disorders. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In addition to measuring blood glucose levels the following blood chemistry tests are also routinely performed: Alkaline Phosphatase; Alanine Amino-Transferase; Albumin; Bilirubin; Phosphorous; Creatinine; BUN = Blood Urea Nitrogen; Calcium; Uric Acid; Sodium; Potassium; and Chloride. In the area of metabolism, targets may be identified for the treatment of diabetes.

Results:

Blood chemistry analysis showed abnormalities in wild-type mice, heterozygous mice and homozygous mice. Urobilinogen was found in 4 of 8 mutant (-/-) mice; nitrites in 2 of 4 (+/+) wild-type mice, 1 of 4 (+/-) heterozygous mice and 4 of 8 (-/-) mice; protein in 2 of 4 (+/+) wild-type mice, 1 of 4 (+/-) mice and 3 of 8 (-/-) mice; and ketone bodies in 2 of 4 (+/+) wild-type mice, 2 of 4 (+/-) heterozygous mice and 5 of 8 mutant (-/-) mice. Increased incidence of protein, nitrites and ketone bodies in the heterozygous (+/-) and homozygous (-/-) mice is related to the abnormal kidney results discovered in the CAT-scan. These results are consistent with CAT-Scan results showing hydronephrosis.

66.42. Generation and Analysis of Mice Comprising DNA82302-2529 (UNQ904) Gene Disruptions

In these knockout experiments, the gene encoding PRO1925 polypeptides (designated as DNA82302-2529) (UNQ904) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: XM_155973 PREDICTED: Mus musculus similar to SARG904 (LOC239691); protein reference: XP_155973 similar to SARG904 [Mus musculus] gi|51769442|ref|XP_358755.2| similar to SARG904 [Mus musculus]; the human gene sequence reference: NM_152459 Homo sapiens hypothetical protein MGC45438 (MGC45438); the human protein sequence corresponds to reference: Q8N2I3 ACCESSION:Q8N2I3 NID: Homo sapiens (Human). Hypothetical protein FLJ90761.

The mouse gene of interest is "similar to SARG904," ortholog of human hypothetical protein MGC45438. Hypothetical protein MGC45438 is a putative secreted protein, consisting of a signal peptide and several weakly predicted, partial conserved domains, such as serpin (serine proteinase inhibitor) domain (SMART accession SM00093), B-cell lymphoma (BCL; anti-apoptotic) domain (SMART accession SM00337), and topoisomerase II domain (SMART accession SM00433). The function of this protein is not known.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for

example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/CS7 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	21	30	15	66
5 Expected	16.5	33	16.5	66
Chi-Sq.= 4.38 Significance= 0.1191674 (hom/n)= 0.19 Avg. Litter Size= 9				

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession BM453823.1).

- 10 1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except bone and stomach, small intestine, and colon.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.42.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA82302-2529 (UNO904))

15 (a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of a human hypothetical protein (MGC45438) resulted in the (-/-) mice exhibiting increased total fat mass and percent total body fat as well as increased total tissue mass. Leukocytes were in 1 of 4 (+/+) wild-type mice and 4 of 8 mutant (-/-) mice. Gene disruption was confirmed by Southern blot.

20 (b) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
 - MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both
- 25 trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImusTM Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

DEXA: Both the male and female (-/-) mice exhibited increased mean total tissue mass, percent total body fat, and total fat mass when compared with their gender-matched (+/+) littermates and the historical means.

These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with obesity. Thus, PRO1925 polypeptides or agonists thereof are essential for normal fat and lipid metabolic processes and especially would be important in the prevention and/or treatment of lipid storage diseases and/or obesity.

5 66.43. Generation and Analysis of Mice Comprising DNA82340-2530 (UNQ905) Gene Disruptions

In these knockout experiments, the gene encoding PRO1926 polypeptides (designated as DNA82340-2530) (UNQ905) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_133749 ACCESSION:NM_133749 NID: gi 19526955 ref NM_133749.1 Mus musculus RIKEN cDNA 2900064A13 gene (2900064A13Rik); protein reference: Q9EP72
10 ACCESSION:Q9EP72 NID: Mus musculus (Mouse). Hypothetical protein (Putative ATG/GTP binding protein precursor); the human gene sequence reference: NM_020154 ACCESSION:NM_020154 NID: gi 9910345 ref NM_020154.1 Homo sapiens chromosome 11 hypothetical protein ORF3 (LOC56851); the human protein sequence corresponds to reference: Q9NPA0 ACCESSION:Q9NPA0 NID: Homo sapiens (Human). Putative ATG/GTP binding protein precursor (HT022).

15 The mouse gene of interest is RIKEN cDNA 2900064A13 gene, ortholog of human C15orf24 (chromosome 15 open reading frame 24). Aliases include c11orf3, HT022, ORF1-FL1, and chromosome 15 hypothetical ATP/GTP binding protein.

C15orf24 is a putative integral plasma membrane protein, containing a signal peptide, a transmembrane segment, and a potential ATP/GTP binding site (O'Brien et al, Biochem Biophys Res Commun 273(1):90-4
20 (2000)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}
25 /C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	23	50	0	73
Expected	18.25	36.5	18.25	73

30 Chi-Sq.= 47.17 Significance= 5.7169585E-11 (hom/n)= 0.0 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_133749.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in
35 all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.43.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA82340-2530 (UNQ905))(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human chromosome 15 open reading frame 24 (C15orf24) resulted in genetic data indicating that this mutation resulted in lethality of homozygous mutants. The male heterozygous mice exhibited an increased anxiety-like response during stress-induced hyperthermia testing.

5 Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

Microscopic: No notable difference was observed in the (+/-) mouse analyzed. However, no (-/-) mice were available for analysis. At 12.5 days, 51 embryos were observed: 27 (+/-) embryos, 10 (+/+) embryos, 12 resorption moles, and 2 inconclusive.

10 Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

Discussion related to embryonic developmental abnormality of lethality:

Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic

15 lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

(c) *Phenotypic Analysis: CNS/Neurology*

20 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not

25 otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders

30 including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type and 4 heterozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

35 These tests included open field to measure anxiety, activity levels and exploration.

Functional Observational Battery (FOB) Test - Stress-induced Hyperthermia:

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general,

short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Results:

5 Stress-Induced Hyperthermia: The male (+/-) mice exhibited increased sensitivity to stress-induced hyperthermia when compared with the level for their gender-matched (+/+) littermates and the historical mean, suggesting an increased anxiety-like response in the mutants.

10 In summary, the functional observation testing revealed a phenotype associated with increased anxiety which could be associated with mild to moderate anxiety, anxiety due to a general medical condition, and/or bipolar disorders; hyperactivity; sensory disorders; obsessive-compulsive disorders, schizophrenia or a paranoid personality. Thus, PRO1926 polypeptides or agonists thereof would be useful in the treatment of such neurological disorders.

66.44. Generation and Analysis of Mice Comprising DNA59844-2542 (UNQ1840) Gene Disruptions

15 In these knockout experiments, the gene encoding PRO3566 polypeptides (designated as DNA59844-2542) (UNQ1840) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_175148 Mus musculus RIKEN cDNA 2300002M23 gene (2300002M23Rik); protein reference: Q8BM15 ACCESSION:Q8BM15 NID: Mus musculus (Mouse). Weakly similar to TASTE bud-specific protein precursor; the human gene sequence reference: NM_014070 Homo sapiens chromosome 6 open reading frame 15 (C6orf15); the human protein sequence corresponds to reference: Q9UIG3
20 ACCESSION:Q9UIG3 NID: Homo sapiens (Human). STG protein.

The mouse gene of interest is RIKEN cDNA 2300002M23 gene, ortholog of human C6orf15 (chromosome 6 open reading frame 15). Aliases include STG and STG protein.

25 C6orf15 is a putative secreted protein, containing a signal peptide and several internal repeats within a major prion protein (PRP) domain. The function of C6orf15 is not known; however, it is expressed in a small subset of taste cells, suggesting that C6orf15 may play a role in taste cell physiology (Neira et al, Mamm Genome 12(1):60-6 (2001); Clark et al, Genome Res 13(10):2265-70 (2003)).

30 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	13	39	21	73
35 Expected	18.25	36.5	18.25	73

Chi-Sq.= 3.68 Significance= 0.15881743 (hom/n)= 0.29 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_175148.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in brain; thymus; spleen; lung; kidney; liver; and stomach, small intestine, and colon among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

5

66.44.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA59844-2542 (UNQ1840)

(a) *OVERALL PHENOTYPIC SUMMARY:*

10 Mutation of the gene encoding the ortholog of human chromosome 6 open reading frame 15 (C6orf15) resulted in the female homozygous mutant mice exhibiting decreased total tissue mass and total body fat when compared with that of their gender-matched wild-type littermates and the historical means. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Bone Metabolism & Body Diagnostics/Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- 15
- DEXA for measurement of bone mineral density on femur and vertebra
 - MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

20 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

25 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

30 DEXA: The female (-/-) mice exhibited decreased mean total tissue mass, percent total body fat, and total fat mass when compared with the levels for their gender-matched (+/+) littermates and the historical means.

These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with growth retardation and/or tissue wasting disorders. Thus, PRO3566 polypeptides or agonists thereof are essential for normal fat and lipid metabolic processes and especially would be important in the prevention and/or treatment of tissue wasting disorders such as cachexia.

35

66.45. Generation and Analysis of Mice Comprising DNA90842-2574 (UNQ1886) Gene Disruptions

In these knockout experiments, the gene encoding PRO4330 polypeptides (designated as DNA90842-2574) (UNQ1886) was disrupted. The gene specific information for these studies is as follows: the mutated mouse

gene corresponds to nucleotide reference: AF168680 ACCESSION:AF168680 NID:6979312 Mus musculus Mus musculus cysteine-rich repeat-containing protein CRIM1 (Crim1); protein reference: Q9JLL0 ACCESSION:Q9JLL0 NID: Mus musculus (Mouse). CYSTEINE-RICH REPEAT-CONTAINING PROTEIN CRIM1 PRECURSOR (FRAGMENT); the human gene sequence reference: NM_016441 ACCESSION:NM_016441 NID:10092638 Homo sapiens Homo sapiens cysteine-rich motor neuron 1 (CRIM1);
 5 the human protein sequence corresponds to reference: Q9NZV1 ACCESSION:Q9NZV1 NID: Homo sapiens (Human). CYSTEINE-RICH REPEAT-CONTAINING PROTEIN S52 PRECURSOR (CRIM1 PROTEIN).

The mouse gene of interest is Crim1 (cysteine-rich motor neuron 1), ortholog of human CRIM1. Aliases include S52 and cysteine-rich repeat-containing protein S52 precursor.

CRIM1 is a type I plasma membrane protein that likely functions as a cell adhesion molecule or receptor.
 10 CRIM1 is also a secreted protein, probably because the extracellular domain is proteolytically cleaved from the plasma membrane. CRIM1 binds with bone morphogenic protein (BMP)-4 and BMP-7 and inhibits BMP signaling (Wilkinson et al, *J Biol Chem* 278(36):34181-8 (2003)). Crim1 is expressed in the developing spinal chord, eye, lens, and testis, potentially playing a role in CNS development and organogenesis (Kolle et al, *Mech Dev* 90(2):181-93 (2000); Lovicu et al, *Mech Dev* 94(1-2):261-5 (2000); Georgas et al, *Dev Dyn* 219(4):582-7 (2000)).
 15 CRIM1 is also expressed in endothelial cells, where it likely plays a role in capillary formation during angiogenesis (Glienke et al, *Mech Dev* 119(2):165-75 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for
 20 example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	14	22	0	36
25 Expected	9	18	9	36

Chi-Sq= 14.85 Significance= 5.9616077E-4 (hom/n)= 0.09 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 5 was targeted (NCBI accession XM_128751.5).

- 30 1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.
 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.45.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA90842-2574 (UNQ1886))

35 (a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human cysteine-rich motor neuron 1 (CRIM1) resulted in genetic data indicating that this mutation resulted in lethality of the homozygous mutants. UNQ1886 is highly expressed in blood vessels and is also involved in regulating bone morphogenic proteins. The heterozygous mice

exhibited an increased mean percentage of B cells in the peripheral blood when compared with their wild-type littermates and the historical mean. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) Pathology

5 Microscopic: At 12.5 days there were 53 embryos observed: 10 (-/-) embryos, 21 (+/-) embryos, 13 (+/+) embryos, and 9 resorption moles. No developmental abnormalities were detected in the 12.5 day embryos by histologic examination.

Gene Expression: LacZ activity was detected only in brain among the panel of tissues analyzed by immunohistochemistry.

UNQ1886 Knockout Embryo Studies:

10 Tissue Embryo studies of the UNQ1886 knockout embryos showed a skin blister and hemorrhagic phenotypes suggesting that UNQ1886 is involved in maintaining tight interaction between two tissue layers. The E12.5 knockout embryo shows skin blisters on both sides of the head (at eye level) as shown by a 6 um FFPE section through the embryo forehead. Skin blisters were also noted in the E13.5 knockout embryo at the back of the skull, mid spine and eye level. Hemorrhage was also noted in the forehead skull. The E14 knockout embryo
15 (14 um frozen section through lacZ stained forehead - level of the ear) shows expression of UNQ186 in the developing skin. Gene 3 beta-gal activity staining of the uterus section of the wholemount uterus showed expression of UNQ1886. Multi-focal hemorrhage in the knockout embryos [E13.5 and E15.5] occurred in the frontal head section [eye and nasal cavity] as well as hemorrhage in the forelimbs and abdomen.

Discussion related to embryonic developmental abnormality of lethality:

20 Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues
25 as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

(c) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury,
30 initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental
35 process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize

antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

Flourescence-activated cell-sorting (FACS) Analysis

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 heterozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

FACS3: The (+/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized

by an increased mean percentage of B cells in the (-/-) mice when compared with that of their (+/+) littermates and the historical mean.

In summary, FACS analysis of immune cell composition indicates that heterozygous (+/-) mice exhibit immunological differences with respect to B cells.

5 66.46. Generation and Analysis of Mice Comprising DNA96893-2621 (UNQ1940) Gene Disruptions

In these knockout experiments, the gene encoding PRO4423 polypeptides (designated as DNA96893-2621) (UNQ1940) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_173375 ACCESSION:NM_173375 NID: gi 27734065 ref NM_173375.1 Mus musculus hypothetical protein B230314O19 (B230314O19); protein reference: Q8BR21
10 ACCESSION:Q8BR21 NID: Mus musculus (Mouse). Hypothetical protein; the human gene sequence reference: NM_205855 Homo sapiens HWKM1940 (UNQ1940); the human protein sequence corresponds to reference: Q6UWF9 ACCESSION:Q6UWF9 NID: Homo sapiens (Human). HWKM1940.

The mouse gene of interest is cDNA sequence BC064033, ortholog of human UNQ1940. Aliases include B230314O19 and HWKM1940.

15 UNQ1940 is a putative 173-amino acid secreted protein, containing a signal peptide and no other defined conserved domain.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for
20 example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	13	30	19	62
25 Expected	15.5	31	15.5	62

Chi-Sq.= 0.68 Significance= 0.7117703 (hom/n)= 0.24 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 2 and 3 were targeted (NCBI accession NM_173375.1).

30 1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

35 66.46.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA96893-2621 (UNQ1940))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of a human putative secreted protein (UNQ1940) resulted in a decreased percentage of CD4 cells and an increased percentage of B cells in the peripheral blood of (-/-) mice. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Flourescence-activated cell-sorting (FACS) Analysis

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included

cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCR β APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

The homozygous (-/-) mice exhibited decreased mean percentages of CD4 cells in the peripheral blood when compared with their (+/+) littermates and the historical means. In addition, the (-/-) mice showed increased percentages of B cells.

In summary, the FACS results indicate that the homozygous mutant mice demonstrate immunological abnormalities marked by decreased T cell populations and increased B cell populations. From these observations, PRO4423 polypeptides or the gene encoding PRO4423 appears to act as a positive regulator of T cell proliferation. But a negative regulator of B cell production. PRO4423 polypeptides and agonists thereof would be important for a healthy immune system and would be useful in stimulating the immune system particularly for increasing T cell proliferation.

66.47. Generation and Analysis of Mice Comprising DNA336539 (UNQ2257) Gene Disruptions

In these knockout experiments, the gene encoding PRO36935 polypeptides (designated as DNA336539) (UNQ2257) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_011627 Mus musculus trophoblast glycoprotein (Tpbg); protein reference: Q9Z0L0 ACCESSION:Q9Z0L0 NID: Mus musculus (Mouse). 5T4 oncofetal trophoblast glycoprotein precursor; the human gene sequence reference: NM_006670 Homo sapiens trophoblast glycoprotein (TPBG); the human protein sequence corresponds to reference: Q13641 ACCESSION:Q13641 NID: Homo sapiens (Human). 5T4 oncofoetal antigen precursor (5T4 oncofetal trophoblast glycoprotein precursor).

The mouse gene of interest is Tpbg (trophoblast glycoprotein), ortholog of human TPBG. Aliases include 5T4, M6P1, 5T4-AG, 5T4-antigen, and 5T4 oncofetal trophoblast glycoprotein.

TPBG is an integral plasma membrane protein, consisting of a signal peptide, several leucine-rich repeats, a transmembrane segment, and a short cytoplasmic C-terminus. TPBG is expressed in trophoblastic cells, amniotic epithelium, brain, ovary, and a variety of carcinomas. TPBG may play a role in processes such as placental and metastasis by modulating cell adhesion, shape, and motility (Ward et al, *J Cell Sci* 116(Pt 22):4533-42 (2003); Shaw et al, *Biochem J* 363(Pt 1):137-45 (2002); King et al, *Biochim Biophys Acta* 1445(3):257-70 (1999); Myers et al, *J Biol Chem* 269(12):9319-24 (1994)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are

intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
5 Observed	23	29	16	68
Expected	17	34	17	68

Chi-Sq.= 4.25 Significance= 0.11943297 (hom/n)= 0.23 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

10 Description: Coding exon 1 was targeted (NCBI accession NM_011627.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in brain, spinal cord, eye, and spleen among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

15 66.47.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA336539 (UNQ2257))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human trophoblast glycoprotein (TPBG) resulted in an increased depressive-like response in tail suspension testing in (-/-) mice. Gene disruption was confirmed by Southern blot.

20 (b) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Functional Observational Battery (FOB) Test - Tail Suspension Testing:

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A

subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Tail Suspension Testing:

5 The tail suspension test is a procedure that has been developed as a model for depressive-like behavior in rodents. In this particular setup, a mouse is suspended by its tail for 6 minutes, and in response the mouse will struggle to escape from this position. After a certain period of time the struggling of the mouse decreases and this is interpreted as a type of learned helplessness paradigm. Animals with invalid data (i.e. climbed their tail during the testing period) are excluded from analysis.

10 Results:

The (-/-) mice exhibited an increased immobility time in the tail suspension testing compared with that of the (+/+) littermates and the historical mean, which is indicative of an increased depressive-like response. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO36935 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

66.48. Generation and Analysis of Mice Comprising DNA62849-2647 (UNQ2420) Gene Disruptions

20 In these knockout experiments, the gene encoding PRO4977 polypeptides (designated as DNA62849-2647) (UNQ2420) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_130887 ACCESSION:NM_130887 NID:18700029 Mus musculus Mus musculus papilin (LOC170721); protein reference: Q9EPX2 ACCESSION:Q9EPX2 NID: Mus musculus (Mouse). PAPILIN; the human gene sequence reference: NM_173462 Homo sapiens papilin, proteoglycan-like sulfated glycoprotein (PAPLN); the human protein sequence corresponds to reference: NP_775733 ACCESSION:NP_775733 NID: gi 50083295 ref NP_775733.2 papilin [Homo sapiens].

25 The mouse gene of interest is Papln (papilin, proteoglycan-like sulfated glycoprotein), ortholog of human PAPLN. Aliases include E030033C16Rik and MGC50452.

30 PAPLN is a secreted protein that associates with extracellular matrix and likely functions as a protease inhibitor (Kramerova et al, 2000). PAPLN consists of a signal peptide, several thrombospondin repeats (extracellular matrix association and cell adhesion; Pfam accession PF00090), a Kunitz/bovine pancreatic trypsin inhibitor domain (indicative of serine protease inhibitors; Pfam accession PF00014), and three C-terminal immunoglobulin domains (protein-protein or protein-ligand interactions; Pfam accession PF00047). PAPLN may play a role in development and organogenesis (Kramerova et al, Development 127(24):5475-85 (2000); Fessler et al, Int J Biochem Cell Biol 36(6):1079-84 (2004); Tucker, Int J Biochem Cell Biol 36(6):969-74 (2004)).

35 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}

/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	27	34	16	77
Expected	19.25	38.5	19.25	77

5 Chi-Sq.= 5.11 Significance= 0.077692226 (hom/n)= 0.2 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 and the preceding noncoding exon was targeted (NCBI accession NM_130887.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.48.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA62849-2647 (UNQ2420))

(a) *OVERALL PHENOTYPIC SUMMARY:*

15 Mutation of the gene encoding the ortholog of human papilin, proteoglycan-like sulfated glycoprotein (PAPLN) resulted in an increased percentage of CD4 cells in the peripheral blood of (-/-) mice. The mutant (-/-) mice also exhibited a trend towards increased prepulse inhibition. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

20 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

25 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

30 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating

cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Flourescence-activated cell-sorting (FACS) Analysis

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

FACS: The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by an increased mean percentage of CD4 cells when compared with their (+/+) littermates and the historical mean. Thus, knocking out the gene which encodes PRO4977 polypeptides causes an increase in the T cell population. From these observations, PRO4977 polypeptides or the gene encoding PRO4977 appears to act as a negative regulator of T cell proliferation. Thus, PRO4977 polypeptides or agonists thereof would be beneficial as a negative regulator of T cell proliferation in those instances wherein a pronounced T-cell proliferation is present such as occurs in autoimmune diseases (for example rheumatoid arthritis patients). In addition, PRO4977 polypeptides would be especially useful in preventing skin graft rejections.

(c) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Prepulse inhibition of the acoustic startle reflex

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB+ 120 dB - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

Results:

The mutant (-/-) mice exhibited a trend towards increased prepulse inhibition of the acoustic startle reflex which is indicative of an enhanced sensorimotor gating/attention.

66.49. Generation and Analysis of Mice Comprising DNA222844 (UNQ2421) Gene Disruptions

In these knockout experiments, the gene encoding PRO4979 polypeptides (also known as PRO38844 polypeptides) (designated as DNA222844) (UNQ2421) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_173182 Mus musculus RIKEN cDNA 1600019O04 gene (1600019O04Rik); protein reference: Q6NWW9 ACCESSION:Q6NWW9 NID: Mus musculus (Mouse). FAD104; the human gene sequence reference: NM_022763 Homo sapiens FAD104 (FAD104); the human protein sequence corresponds to reference: Q8IXB2 ACCESSION:Q8IXB2 NID: Homo sapiens (Human). FAD104.

The mouse gene of interest is RIKEN cDNA 1600019O04 gene, ortholog of human FAD104 (factor for adipocyte differentiation 104). Aliases include FLJ23399 and DKFZp762K137.

FAD104 is a putative integral plasma membrane protein that likely functions as a receptor or cell adhesion molecule. The protein contains nine fibronectin type III domains and a C-terminal transmembrane segment. FAD104 may play a role in adipogenesis (Tominaga et al, FEBS Lett 577(1-2):49-54 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
10 Observed	17	36	1	54
Expected	13.5	27	13.5	54

Chi-Sq.= 20.47 Significance= 3.5891873E-5 (hom/n)= 0.08 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

15 Description: Coding exon 1 was targeted (NCBI accession NM_173182.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

20 66.49.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA222844 (UNQ2421))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human factor for adipocyte differentiation 104 (FAD104) resulted in genetic data indicating that this mutation resulted in lethality of the homozygous mutants. The heterozygous mice exhibited an increased mean serum IgG2a level when compared with that of their wild-type littermates. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

Genetics: Homozygous lethal. The (-/-) pups were dead at the time of genotyping.

Microscopic: No developmental abnormalities were detected in the 12.5 d embryos by histologic examination.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

30 *Discussion related to embryonic developmental abnormality of lethality:*

Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

(c) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

Serum Imm. 2: The (+/-) mice exhibited an increased mean serum IgG2a level when compared with that of their (+/+) littermates, the (+/+) mice for the project run, and the historical median.

Heterozygous (+/-) mice exhibited elevation of IgG2a serum immunoglobulins compared to their gender-matched (+/+) littermates. IgG2a efficiently opsonizes pathogens for engulfment by phagocytes and activates the complement system. The observed phenotype suggests that the PRO4979 polypeptide is a negative regulator of inflammatory responses.

66.50. Generation and Analysis of Mice Comprising DNA97003-2649 (UNQ2422) Gene Disruptions

In these knockout experiments, the gene encoding PRO4980 polypeptides (designated as DNA97003-2649) (UNQ2422) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_177648 Mus musculus transmembrane protein 15 (Tmem15); protein reference: Q8R2Y3 ACCESSION:Q8R2Y3 NID: Mus musculus (Mouse). Similar to KIAA1094 protein; the human gene sequence reference: NM_014908 Homo sapiens transmembrane protein 15 (TMEM15); the human protein sequence corresponds to reference: Q9UPQ8 ACCESSION:Q9UPQ8 NID: Homo sapiens (Human). Hypothetical protein KIAA1094.

The mouse gene of interest is Tmem15 (transmembrane protein 15), ortholog of human TMEM15. Aliases include MGC36683, mKIAA1094, cDNA sequence BC026973, and KIAA1094.

TMEM15 is a likely integral plasma membrane protein, consisting of a signal peptide and 11 to 14 transmembrane segments within a weakly predicted actin-like ATPase domain (SCOP).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	33	0	51
Expected	12.75	25.5	12.75	51

Chi-Sq.= 41.74 Significance= 8.6352275E-10 (hom/n)= 0.0 Avg. Litter Size= 7

30 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_177648.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except bone.

35 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.50.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA97003-2649 (UNQ2422))(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human transmembrane protein 15 (TMEM15) resulted in genetic data indicating that this mutation resulted in lethality of the homozygous mutants. The heterozygous mice exhibited a decreased depressive-like response: Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

Microscopic: Not tested due to embryonic lethality. At 12.5 days, there were 39 embryos observed: 23 (+/-) embryos, 11 (+/+) embryos, 3 to-be-determined, and 2 inconclusive. Wholemount data at 7.5 dpc and 12.5 dpc shows broad and ubiquitous staining in the wildtype embryos. There is strong LacZ staining in the extraembryonic ectoderm at 6.5 dpc and 7.5 dpc in the heterozygous (+/-) embryos.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

Discussion related to embryonic developmental abnormality of lethality:

Embryonic lethality in knockout mice usually results from various serious developmental problems including but not limited to neuro-degenerative diseases, angiogenic disorders, inflammatory diseases, or where the gene/protein has an important role in basic cell signaling processes in many cell types. In addition, embryonic lethals are useful as potential cancer models. Likewise, the corresponding heterozygous (+/-) mutant animals are particularly useful when they exhibit a phenotype and/or a pathology report which reveals highly informative clues as to the function of the knocked-out gene. For instance, EPO knockout animals were embryonic lethals, but the pathology reports on the embryos showed a profound lack of RBCs.

(c) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type and 4 heterozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Functional Observational Battery (FOB) Test - Tail Suspension Testing:

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A

subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Tail Suspension Testing:

5 The tail suspension test is a procedure that has been developed as a model for depressive-like behavior in rodents. In this particular setup, a mouse is suspended by its tail for 6 minutes, and in response the mouse will struggle to escape from this position. After a certain period of time the struggling of the mouse decreases and this is interpreted as a type of learned helplessness paradigm. Animals with invalid data (i.e. climbed their tail during the testing period) are excluded from analysis.

10 Results:

Tail Suspension2: The (+/-) mice exhibited decreased immobility time during tail suspension testing when compared with their (+/+) littermates and the historical mean, suggesting a decreased depressive-like response in the mutants.

15 Thus, heterozygous mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO4980 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

20 66.51. Generation and Analysis of Mice Comprising DNA94849-2960 (UNQ2423) Gene Disruptions

In these knockout experiments, the gene encoding PRO4981 polypeptides (designated as DNA94849-2960) (UNQ2423) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_027379 Mus musculus male sterility domain containing 2 (Mlstd2); protein reference: Q922J9 ACCESSION:Q922J9 NID: Mus musculus (Mouse). RIKEN cDNA 3732409C05 gene; the human gene sequence reference: NM_032228 Homo sapiens male sterility domain containing 2 (MLSTD2); 25 the human protein sequence corresponds to reference: Q8WVX9 ACCESSION:Q8WVX9 NID: Homo sapiens (Human). Similar to RIKEN cDNA 3732409C05 gene.

The mouse gene of interest is Mlstd2 (male sterility domain containing 2), ortholog of human MLSTD2. Aliases include FAR1, 2600011M19Rik, 3732409C05Rik, FAR1, FLJ22728, and fatty acyl CoA reductase 1.

30 MLSTD2 is a peroxisomal enzyme that catalyzes the formation of fatty alcohols by reducing fatty acyl-CoA with co-substrate NADPH, preferring unsaturated fatty acids of 16 or 18 carbons. The enzyme is expressed primarily in preputial gland, a type of sebaceous gland, and in brain, a lipid ether-rich tissue. MLSTD2 likely plays a role in the biosynthesis of wax monoesters and lipid ethers (Cheng and Russell, J Biol Chem 279(36):37789-97 (2004)).

35 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I

phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	30	16	64
Expected	16	32	16	64

Chi-Sq.= 3.51 Significance= 0.17290725 (hom/n)= 0.31 Avg. Litter Size= 8

5 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_027379.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in brain, spinal cord, eye, thymus, spleen, lung, and kidney among the 13 adult tissue samples tested by RT-PCR.

10 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.51.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA94849-2960 (UNQ2423))

(a) *OVERALL PHENOTYPIC SUMMARY:*

15 Mutation of the gene encoding the ortholog of human male sterility domain containing 2 (MLSTD2) resulted in the homozygous mutant mice exhibiting a hearing impairment. The knockout (-/-) mice also showed an increased stress-induced hyperthermia and a trend towards an enhanced circadian rhythm. Microscopic analysis revealed testicular degeneration in the male mutants, consistent with the infertility noted diagnostically. In addition, decreased bone mineral content and density measurements were observed in the homozygous mutant mice, along with notably increased body fat in the female mutants. Disruption of the target gene was confirmed by Southern
20 hybridization analysis.

(b) *Pathology*

Gross: The 2 male (-/-) mice available for analysis exhibited significantly decreased testis weight in male knockouts.

25 Microscopic: The 2 male (-/-) mice analyzed (M-214 and M-226) exhibited marked testicular degeneration characterized by large multinuclear giant cells in the seminiferous tubules and no sperm in the epididymides. The hepatocytes had cytoplasmic vacuoles characteristic of glycogen accumulation of marked and moderate intensity in the females but slight in the males.

Gene Expression: LacZ activity was detected in testes among the panel of tissues analyzed by immunohistochemistry.

30 (c) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not
35 limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar

disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

5 Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. *Prepulse inhibition of the acoustic startle reflex*

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB+ 120 dB - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

15 Results:

PPI: Only 3/8 (-/-) mice lacked a startle response, suggesting a hearing impairment in the mutants.

Functional Observational Battery (FOB) Test - Stress-induced Hyperthermia:

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Results:

25 Stress-Induced Hyperthermia: The (-/-) mice exhibited an increased stress-induced hyperthermia when compared with the value for their gender-matched (+/+) littermates and the historical mean, suggesting a increased anxiety-like response in the mutants. These results are consistent with the circadian rhythm neurological testing. Thus, PRO4981 polypeptides or agonists thereof would be useful in the treatment of anxiety related disorders.

Circadian Test Description:

30 Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The (-/-) mice exhibited increased ambulatory counts during the 12-hour habituation period of home-cage activity testing when compared with their gender-matched (+/+) littermates and the historical mean.

These results demonstrate an enhanced circadian rhythm. Home-cage activity testing is also suggestive of increased activity or hyperactivity which could be related to an anxiety-like response.

(d) *Cardiology/Blood Pressure and Heart Rate*

Description:

5 Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days.

Blood Pressure Results:

The (-/-) mouse exhibited decreased systolic blood pressure when compared to its gender-matched (+/+) littermates and the historical mean.

(e) *Phenotypic Analysis: Metabolism -Blood Chemistry*

10 In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In addition to measuring blood glucose levels the following blood chemistry tests are also routinely performed: Alkaline Phosphatase; Alanine Amino-Transferase; Albumin; Bilirubin; Phosphorous; Creatinine; BUN = Blood Urea Nitrogen; Calcium; Uric Acid; Sodium; Potassium; and
15 Chloride. In the area of metabolism, targets may be identified for the treatment of diabetes.

Results:

Blood Chemistry: Both male and female the (-/-) mice exhibited a decreased mean serum calcium level. The decreased calcium levels is consistent with the observation of decreased bone mineral content and density measurements.

20 (f) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited
25 to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.
30

Results:

Blood Glucose Levels/Glucose Tolerance Test:

The (-/-) mice exhibited a significantly impaired glucose tolerance when placed on a high fat diet
35 compared with their gender-matched (+/+) littermates and the historical means.

These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose

homeostasis, and therefore PRO4981 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

(g) *Bone Metabolism & Body Diagnostics*

(1) Tissue Mass & Lean Body Mass Measurements - Dexa

5

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

10 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

15 Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

Body Weight and Length: The male (-/-) mice exhibited decreased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean.

20 Fertility: The male (-/-) mouse available for analysis produced no pups after 40 days of breeding and 4 matings with female (+/+) mice.

(2) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- 25 • MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

30 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

35 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1

femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebrae trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male and female (-/-) mice exhibited decreased mean lean body mass, bone mineral content, and bone mineral density in total body and vertebrae when compared with that of their gender-matched (+/+) littermates and the historical means. The female (-/-) mice also exhibited an increased mean total tissue mass and slight increase in total fat mass, and percent total body fat.

Micro CT: The male (-/-) mice exhibited decreased mean femoral mid-shaft cross-sectional area when compared with that of their gender-matched (+/+) littermates and the historical mean.

The (-/-) mice analyzed by DEXA and bone micro CT analysis exhibited decreased bone measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders. However, the mutant (-/-) mice also exhibited decreased body weight and length and lean body mass as well as infertility in male (-/-) mice. On the other hand, female (-/-) mice exhibited a slight increase in mean percentage of body fat. These observations suggest that for the most part male mutant mice deficient in the gene which encodes PRO4981 polypeptides leads to metabolic disorders associated with growth retardation in (-/-) mice but also abnormal bone measurements reflective of osteoporosis. Thus, PRO4981 polypeptides or agonists thereof would be useful in the treatment of bone related disorders such as osteoporosis or would be useful in maintaining bone homeostasis. Antagonists (or inhibitors) of PRO4981 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with abnormal bone metabolism including arthritis, osteoporosis and osteopenia.

66.52. Generation and Analysis of Mice Comprising DNA115291-2681 (UNQ2501) Gene Disruptions

In these knockout experiments, the gene encoding PRO5801 polypeptides (designated as DNA115291-2681) (UNQ2501) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: BC026546 Mus musculus interleukin 17 receptor B, mRNA (cDNA clone MGC:35924 IMAGE:5042466); protein reference: Q9JIP3 ACCESSION:Q9JIP3 NID: Mus musculus (Mouse). INTERLEUKIN-17B RECEPTOR PRECURSOR (IL-17B RECEPTOR) (IL-17 RECEPTOR HOMOLOG 1) (IL-17RH1) (IL17RH1) (IL-17ER); the human gene sequence reference: NM_018725 Homo sapiens interleukin 17 receptor B (IL17RB), transcript variant 1; the human protein sequence corresponds to reference: Q9NRM6 ACCESSION:Q9NRM6 NID: Homo sapiens (Human). INTERLEUKIN-17B RECEPTOR PRECURSOR (IL-17B RECEPTOR) (IL-17 RECEPTOR HOMOLOG 1) (IL-17RH1) (IL17RH1) (CYTOKINE RECEPTOR CRL4).

The mouse gene of interest is Il17rb (interleukin 17 receptor B), ortholog of human IL17RB. Aliases include Evi27, Il17br, IL-17ER, IL17RH1, IL-17Rh1, CRL4, MGC5245, IL-17B receptor, cytokine receptor

CRL4, interleukin 17B receptor, interleukin 17 receptor homolog, interleukin 17 receptor homolog 1, and ecotropic viral integration site 27.

IL17RB is a type I plasma membrane protein that functions as a receptor for cytokines IL17E and IL17B. The receptor is capable of activating nuclear factor kappaB and stimulating production of proinflammatory chemokine IL-8. IL17RB is expressed in liver, kidney, pancreas, testis, colon, brain, and small intestine. IL17RB likely plays a role in inflammation and may participate in various disease processes, such as rheumatoid arthritis, psoriasis, multiple sclerosis, tumor growth promotion, and transplant rejection (Lee et al, *J Biol Chem* 276(2):1660-4 (2001); Tian et al, *Oncogene* 19(17):2098-109 (2000); Shi et al, *J Biol Chem* 275(25):19167-76 (2000); Moseley et al, *Cytokine Growth Factor Rev* 14(2):155-74 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	19	34	24	77
Expected	19.25	38.5	19.25	77

Chi-Sq.= 2.18 Significance= 0.33621648 (hom/n)= 0.29 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 4 were targeted (NCBI accession NM_019583.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle, bone, and heart.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.52.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA115291-2681 (UNQ2501)

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human interleukin 17 receptor B (IL17RB) resulted in the (-/-) mice exhibited an enhanced glucose tolerance. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose

tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Glucose Tolerance Test: The male mutant (-/-) mice on a high fat diet exhibited an enhanced glucose tolerance when compared with their gender-matched (+/+) littermates.

In these studies the mutant (-/-) mice showed an increased or enhanced glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mice exhibited an increased insulin sensitivity or the opposite phenotypic pattern of an impaired glucose homeostasis, and as such antagonists (inhibitors) to PRO5801 polypeptides or its encoding gene would be useful in the treatment of an impaired glucose homeostasis.

66.53. Generation and Analysis of Mice Comprising DNA96988-2685 (UNQ2507) Gene Disruptions

In these knockout experiments, the gene encoding PRO5995 polypeptides (designated as DNA96988-2685) (UNQ2507) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_146241 ACCESSION:NM_146241 NID: gi 22122816 ref NM_146241.1 Mus musculus thyrotropin-releasing hormone degrading ectoenzyme (Trhde-pending); protein reference: Q8K093 ACCESSION:Q8K093 NID: Mus musculus (Mouse). Hypothetical protein; the human gene sequence reference: NM_013381 ACCESSION:NM_013381 NID: gi 7019560 ref NM_013381.1 Homo sapiens thyrotropin-releasing hormone degrading ectoenzyme (TRHDE); the human protein sequence corresponds to reference: Q6UWJ4 ACCESSION:Q6UWJ4 NID: Homo sapiens (Human). TRHDE.

The mouse gene of interest is Trhde (thyrotropin-releasing hormone degrading ectoenzyme), ortholog of human TRHDE. Aliases include MGC40831, 9330155P21Rik, PAP-II, pyroglutamyl-peptidase II, TRH-degrading ectoenzyme, TRH-DE, TRH-specific aminopeptidase, and thyroliberinase.

TRHDE is an extracellular type II plasma membrane protein and zinc metalloprotease that catalyzes the removal of the N-terminal pyroglutamyl group from thyrotropin-releasing hormone (TRH). TRHDE likely plays a role in TRH signaling by inactivating the neuropeptide after its release. TRHDE is expressed primarily in brain but is also expressed in heart, lung, liver, skeletal muscle, and serum (Baeza et al, *Life Sci* 68(17):2051-60 (2001); Schomburg et al, *Eur J Biochem* 265(1):415-22 (1999); Kelly et al, *J Biol Chem* 275(22):16746-51 (2000); Schmitmeier et al, *Eur J Biochem* 269(4):1278-86 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	27	35	27	89
Expected	22.25	44.5	22.25	89

Chi-Sq.= 0.98 Significance= 0.6126264 (hom/n)= 0.27 Avg. Litter Size= 10

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_146241.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except lung, skeletal muscle, bone, and adipose.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.53.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA96988-2685 (UNQ2507))

(a) *OVERALL PHENOTYPIC SUMMARY:*

- 10 Mutation of the gene encoding the ortholog of human thyrotropin-releasing hormone degrading ectoenzyme (TRHDE) resulted in the mutant (-/-) mice exhibiting decreased mean body weight and length as well as decreased total tissue mass and lean body mass. Tail suspension testing showed increased immobility in the (-/-) mice. Gene disruption was confirmed by Southern blot.

(b) *Bone Metabolism & Body Diagnostics*

- 15 (1) Tissue Mass & Lean Body Mass Measurements - Dexa

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

- 20 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

- 25 Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

Body Weight and Length: The male (-/-) mice exhibited decreased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean.

- 30 (2) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
 - MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.
- 35

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized

animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The male (-/-) mice exhibited decreased mean total tissue mass and lean body mass when compared with that of their gender-matched (+/+) littermates and the historical means.

Thus mutant (-/-) mice show a negative phenotype marked by decreased body weights and body length and total tissue mass and lean body mass which can be due to growth retardation or a tissue-wasting condition such as cachexia. Thus, antagonists or inhibitors of PRO5995 polypeptides or its encoding gene would mimic these abnormal metabolic related effects. On the other hand, PRO5995 polypeptides or agonists thereof would be useful in the prevention and/or treatment of such metabolic disorders as cachexia or other tissue wasting diseases as well as being important for normal growth development

(c) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Functional Observational Battery (FOB) Test - Tail Suspension Testing:

5 The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Tail Suspension Testing:

10 The tail suspension test is a procedure that has been developed as a model for depressive-like behavior in rodents. In this particular setup, a mouse is suspended by its tail for 6 minutes, and in response the mouse will struggle to escape from this position. After a certain period of time the struggling of the mouse decreases and this is interpreted as a type of learned helplessness paradigm. Animals with invalid data (i.e. climbed their tail during the testing period) are excluded from analysis.

Results:

15 Tail Suspension2: The (-/-) mice exhibited increased immobility time when compared with the value for their (+/+) littermates and the historical mean, which is indicative of a depressive-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO5995 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

66.54. Generation and Analysis of Mice Comprising DNA98380 (UNQ2512) Gene Disruptions

In these knockout experiments, the gene encoding PRO6001 polypeptides (designated as DNA98380) (UNQ2512) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene
25 corresponds to nucleotide reference: NM_133187 ACCESSION:NM_133187 NID: gi 18875327 ref NM_133187.1 Mus musculus RIKEN cDNA 1110032E23 gene (1110032E23Rik); protein reference: Q9ET25 ACCESSION:Q9ET25 NID: Mus musculus (Mouse). Hypothetical basic protein I-19; the human gene sequence reference: NM_016613 Homo sapiens hypothetical protein DKFZp434L142 (DKFZp434L142); the human protein sequence corresponds to reference: Q6UWH4 ACCESSION:Q6UWH4 NID: Homo sapiens (Human). TCPD2512.

30 The mouse gene of interest is RIKEN cDNA 1110032E23 gene, ortholog of human hypothetical protein DKFZp434L142. Aliases include AD021 and AD036.

Hypothetical protein DKFZp434L142 is a putative 517-amino acid protein, containing no conserved domains except for a transmembrane segment near the N terminus.

35 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I

phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	43	21	82
Expected	20.5	41	20.5	82

Chi-Sq.= 8.57 Significance= 0.013773624 (hom/n)= 0.24 Avg. Litter Size= 9

5 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_133187.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

10 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.54.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA98380 (UNQ2512))

(a) *OVERALL PHENOTYPIC SUMMARY:*

15 Mutation of the gene encoding the ortholog of a human hypothetical protein (DKFZp434L142) resulted in impaired glucose tolerance in (-/-) mice. Male (-/-) mice also exhibited a decreased basal body temperature. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

20 In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

25 Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

30 Blood Glucose Levels/Glucose Tolerance Test:

The (-/-) mice exhibited impaired glucose tolerance when placed on a high fat diet compared with their gender-matched (+/+) littermates and the historical means.

35 These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose homeostasis, and therefore PRO6001 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

66.55. Generation and Analysis of Mice Comprising DNA105680-2710 (UNQ2543) Gene Disruptions

In these knockout experiments, the gene encoding PRO6095 polypeptides (designated as DNA105680-2710) (UNQ2543) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_153528 Mus musculus RIKEN cDNA 4921521N14 gene (4921521N14Rik); protein reference: Q8CI52 ACCESSION:Q8CI52 NID: Mus musculus (Mouse). RIKEN cDNA 4921521N14; the human gene sequence reference: BC035040 Homo sapiens hypothetical protein DKFZp434C0328; the human protein sequence corresponds to reference: Q8IYS0 ACCESSION:Q8IYS0 NID: Homo sapiens (Human). DKFZp434C0328 protein.

The mouse gene of interest is RIKEN cDNA 4921521N14 gene, ortholog of human hypothetical protein DKFZp434C0328. Aliases include MGC47315.

Hypothetical protein DKFZp434C0328 is a putative membrane protein, consisting of a GRAM domain, a transmembrane segment, and a potential glycosylphospholipid (GPI) anchor site. GRAM domains are found in proteins such as glucosyltransferases, myotubularins, and other membrane-associated proteins and are likely to function in membrane targeting (Doerks et al, Trends Biochem Sci 25(10):483-5 (2000)). The cell location of hypothetical protein DKFZp434C0328 is ambiguous. The transmembrane segment suggests that the hypothetical protein may be an integral membrane protein, whereas the GPI anchor site suggests that the protein may be associated with the extracellular surface of the plasma membrane. Because GRAM domains may be involved in association of proteins with target membranes (Oku et al, EMBO J 22(13):3231-41 (2003)), hypothetical protein DKFZp434C0328 may be located on intracellular membranes.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	20	30	18	68
Expected	17	34	17	68

Chi-Sq.= 1.86 Significance= 0.39455372 (hom/n)= 0.29 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_153528.1).

1. Wild-type Expression Panel: Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone.

QC Images: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.55.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA105680-2710 (UNQ2543))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of a human hypothetical protein (DKFZp434C0328) resulted

in immunological abnormalities in (-/-) mice. The homozygous mutant mice exhibited increased IgM+, IgD+ B cells, and B220hi CD43- cells in bone marrow when compared with the levels for their wild-type littermates. In addition, the mutant (-/-) mice showed increased total tissue mass and fat content (accompanied by elevated cholesterol levels) with increased body weight and length as well as increased bone-mineral density measurements. Disruption of the target gene was confirmed by Southern hybridization analysis.

5 (b) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides.

10 *Blood Lipids*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The male (-/-) mice exhibited an increased mean serum cholesterol level when compared with that of their gender-matched (+/+) littermates and the historical mean.

20 As summarized above, the (-/-) mice exhibited increased mean serum cholesterol levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO6095 gene can serve as a model for cardiovascular disease. PRO6095 polypeptides or its encoding gene would be useful in regulating blood lipids such as cholesterol. Thus, PRO6095 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, diabetes and/or obesity.

25 (c) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

30 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex

(MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

Flourescence-activated cell-sorting (FACS) Analysis

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

Tissue Specific FACS-Project: The (-/-) mice exhibited increased IgM+, IgD+ B cells, and B220hi CD43- cells in bone marrow when compared with those of their (+/+) littermates. Mature naive B cells co-express IgM and

IgD and leave the bone marrow to circulate through the lymphoid organs. By knocking out the gene encoding PRO6095 polypeptides, the mutant (-/-) mice exhibited increased percentages of B cell progenitors as well as the immunoglobulins that are expressed by these cells. Thus, PRO6095 polypeptides appear to act as a negative regulator for B cell differentiation and/or proliferation. Antagonists (inhibitors) of PRO6095 polypeptides would be useful in the stimulation of B cell production.

5 *Serum Immunoglobulin Isotyping Assay:*

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

10 Results:

The (-/-) mice exhibited increased mean serum IgG3 levels compared to their gender-matched (+/+) littermate controls, the (+/+) mice for the project run and the historical median.

The serum immunoglobulin isotyping assay revealed that homozygous adults exhibited increased serum IgG3 levels. Thus, homozygotes showed elevated serum immunoglobulins compared with the (+/+) littermates. IgG3 immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. These immunological abnormalities suggest that antagonists or inhibitors of PRO6095 polypeptides would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO6095 polypeptides or agonists thereof would inhibit the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(d) *Bone Metabolism & Body Diagnostics*

(1) Tissue Mass & Lean Body Mass Measurements - DEXA

Dexa Analysis - Test Description:

25 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

35 Results:

Body Weight and Length: The male (-/-) mice exhibited increased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean.

(2) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

5 *Dexa Analysis - Test Description:*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

10 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

15 *Bone microCT Analysis:*

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple
20 bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

25 DEXA: The male (-/-) mice exhibited increased mean total tissue mass, total fat mass, and percent total body fat when compared with those of their gender-matched (+/+) littermates and the historical means.

Micro CT: The male (-/-) mice exhibited increased mean vertebral trabecular bone connectivity density when compared with the levels for their gender-matched (+/+) littermates and the historical means.

30 These results demonstrate that knockout mutant mice exhibit abnormal bone metabolism with increased mean vertebral trabecular bone measurements similar to osteopetrosis characterized by increase in bone mass density. Thus, it appears that PRO6095 polypeptides or agonists thereof would be useful in maintaining bone homeostasis and for bone remodeling by balancing osteoclast and osteoblast activity. In addition, antagonists or inhibitors PRO6095 polypeptides or its encoding gene would be useful in bone healing or for the treatment of other bone related abnormalities associated with increased bone mineralization.

35 The (-/-) mice also exhibited increased mean total tissue mass and increased mean percent total body fat and total fat mass when compared with their gender-matched (+/+) littermates and the historical means. These findings are consistent with the increased mean body weight and length exhibited by the (-/-) mutant mice.

These studies show that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that is

associated with obesity. Thus, PRO6095 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be useful in the prevention and/or treatment of lipid storage diseases and/or obesity.

66.56. Generation and Analysis of Mice Comprising DNA110700-2716 (UNQ2553) Gene Disruptions

5 In these knockout experiments, the gene encoding PRO6182 polypeptides (designated as DNA110700-2716) (UNQ2553) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_020003 ACCESSION:NM_020003 NID: gi 9910457 ref NM_020003.1 Mus musculus RIKEN cDNA 0610031J06 gene (0610031J06Rik); protein reference: Q9JHJ3 ACCESSION:Q9JHJ3 NID: Mus musculus (Mouse). Kidney predominant protein (RIKEN cDNA 0610031J06 gene); the human gene sequence reference: NM_144580 ACCESSION:NM_144580 NID: gi 24307870 ref NM_144580.1 Homo sapiens hypothetical protein MGC31963 (MGC31963); the human protein sequence corresponds to reference: Q8WWB7 ACCESSION:Q8WWB7 NID: Homo sapiens (Human). Hypothetical protein NT2RP1000567.

15 The mouse gene of interest is RIKEN cDNA 0610031J06 gene, ortholog of human MGC31963 (kidney predominant protein NCU-G1). Aliases include NCU-G1.

MGC31963 is a putative type I integral plasma membrane protein, containing a signal peptide and a transmembrane segment near the C-terminus. The protein is expressed at high levels in the kidney cortex and at lower levels in several other tissues (Kawamura et al, Biochem Genet 39(1-2):33-42 (2001); Clark et al, Genome Res 13(10):2265-70 (2003)).

20 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	24	40	13	77
Expected	19.25	38.5	19.25	77

Chi-Sq.= 0.53 Significance= 0.76720595 (hom/n)= 0.26 Avg. Litter Size= 9

30 Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 6 were targeted (NCBI accession NM_020003.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

35 2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.56.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA110700-2716 (UNQ2553))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human kidney predominant protein NCU-G1 (MGC31963) resulted in hepatitis in (-/-) mice. The homozygous mutant mice exhibited signs of anemia and immunological abnormalities when compared with the levels for their wild-type littermates and the historical means. In addition, both the male and female homozygous mutant mice exhibited increased mean serum alkaline phosphatase levels and decreased mean serum glucose levels. The (-/-) mice also exhibited decreased vBMD and BMD in total body as well as decreased mean vertebral trabecular number and connectivity density. The (-/-) mice showed a trend towards increased prepulse inhibition. The livers of the mutants were smaller than normal upon gross examination; microscopic analysis revealed mild-to-moderate necrotizing hepatitis. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

Gross: The livers of the (-/-) mice were smaller than normal, and the hepatic capsular surface was irregular and pitted due to the underlying loss/collapse of parenchyma.

Microscopic: The (-/-) mice analyzed exhibited mild-to-moderate multifocal necrotizing hepatitis, characterized by minimal ongoing hepatocellular necrosis and degeneration. Minimal-to-mild subacute and active inflammatory infiltrates were also present in areas of parenchymal loss. Multifocally, there were clusters of hematopoietic cells (granulocytic) in the liver and diffuse hyperplasia of granulocytic precursors, with concurrent decreases in erythroid cell precursors, in the spleen and bone marrow. The minimal hepatic fibrosis present in these mutants reflect the known decreased hepatic fibrogenic response of C57Bl/6 mice to hepatic injury.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Pathology/CAT Scan*

CAT-Scan Protocol:

Mice were injected with a CT contrast agent, Omnipaque 300 (Nycomed Amersham, 300 mg of iodine per ml, 0.25ml per animal, or 2.50-3.75 g iodine/kg of body weight) intraperitoneally. After resting in the cage for ~ 10 minutes, the mouse was then sedated by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight). A CAT-scan was performed using a MicroCAT scanner (ImTek, Inc.) with the anesthetized animal lying prone on the test bed. Three dimensional images were reconstructed by the Feldkamp algorithm in a cluster of workstations using an ImTek 3D RECON software.

Results:

CATScan: All 3 (-/-) mice analyzed (M-218, M-249, and F-254) exhibited reduced liver size.

(d) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different

biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

5 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic
10 T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

15 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

20 In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

25 The following tests were performed:

(1) *Hematology Analysis:*

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

30 Results:

(1) Hematology (platelet count):

The (-/-) mice exhibited a notably decreased mean platelet count and increased mean platelet volume when compared with their (+/+) littermates and the historical mean.

35 Thus, mutant mice deficient in the DNA110700-2716 gene resulted in a phenotype related to coagulation disorders. In this regard, PRO6182 polypeptides or agonists thereof would be useful in treating disorders related to abnormal blood coagulation such as hemophilia.

(2) Hematology (red blood cell & hemoglobin):

The (-/-) mice also exhibited decreased mean total white blood cell and absolute lymphocyte counts and

an increased mean absolute monocyte count when compared with the levels for their (+/+) littermates and the historical means. The (-/-) mice also exhibited signs of anemia, including a decreased mean red blood cell count, hemoglobin concentration, and hematocrit and an increased red cell distribution width when compared with their (+/+) littermates and the historical means.

5 These results are related to a phenotype associated with anemia as well as a depressed immune system. Thus, PRO6182 polypeptides, agonists thereof or the encoding gene for PRO6182 polypeptides must be essential for normal red blood cell production and as such would be useful in the treatment of blood disorders associated with anemia or a low hematocrit. In addition, the (-/-) mice exhibit an impaired lymphocyte count important for the adaptive immune response.

(2) *Serum Immunoglobulin Isotyping Assay:*

10 The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

15 Serum Imm. 2: The (-/-) mice exhibited decreased mean serum IgG1, IgG2a, IgG2b, and IgG3 levels when compared with those of their (+/+) littermates, the (+/+) mice in the project run, and the historical medians.

The serum immunoglobulin isotyping assay revealed that hemizygous mutant adults exhibited decreased serum IgG immunoglobulin levels. Thus, homozygous (-/-) mice showed an abnormally low serum immunoglobulins compared with the (+/+) littermates. Thus, the gene encoding PRO6182 is essential for making immunoglobulins (or gamma globulins). Gamma globulins have neutralization effects and to a lesser extent are important for activation of the complement system. These immunological abnormalities suggest that PRO6182 polypeptides or agonists thereof would be useful in stimulating the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, inhibitors (antagonists) of PRO6182 polypeptides would inhibit the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(3) *Flourescence-activated cell-sorting (FACS) Analysis*

Procedure:

30 FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each

mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCR β APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

5 FACS3: The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by a decreased mean percentage of CD8 cells and an increased mean percentage of monocytes when compared with the levels for their (+/+) littermates.

Tissue Specific FACS-Mouse: The (-/-) mice exhibited increased CD11b+CD11c- cells in spleen when compared with that of their (+/+) littermates.

10 In summary, the (-/-) mice exhibited increased IgM+, IgD+, and B220hi CD43- cells in bone marrow when compared with those of their (+/+) littermates. Mature naive B cells co-express IgM and IgD and leave the bone marrow to circulate through the lymphoid organs. By knocking out the gene encoding PRO6095 polypeptides, the mutant (-/-) mice exhibited increased percentages of B cell progenitors as well as the immunoglobulins that are expressed by these cells. Thus, PRO6095 polypeptides appear to act as a negative regulator for B cell differentiation and/or proliferation. In addition, the (-/-) mice exhibited a decreased mean
15 percentage of CD8 cells. CD8 proteins are the co-receptor molecules which bind/recognize the MHC Class I molecules for cooperation with the T cell receptor in antigen recognition.

(4) *Acute Phase Response:*

20 Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sub-lethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNF α , MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

25 The (+/-) mice exhibited increased mean serum TNF-alpha, MCP-1 and especially IL-6 responses to LPS challenge when compared with their (+/+) littermates and the historical means.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO6182 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (TNF-alpha, MCP-1 and IL-6 production) when challenged with the LPS endotoxin indicating a pro-inflammatory response. TNF-alpha, MCP-1 and IL-6 contribute to the later stages of B cell activation. TNF-alpha is an important inflammatory mediator. In addition, both TNF-alpha, MCP-1 and IL-6 play a critical role in inducing the acute phase response and systemic inflammation. TNF-alpha can substitute for the membrane-bound signal in macrophage activation (thus serving as an effector molecule).

(e) *Phenotypic Analysis: Metabolism -Blood Chemistry*

35 In the area of metabolism, targets may be identified for the treatment of diabetes or other metabolic disorders. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In addition to measuring blood glucose levels the following blood chemistry tests are also routinely performed: Alkaline Phosphatase; Alanine Amino-

Transferase; Albumin; Bilirubin; Phosphorous; Creatinine; BUN = Blood Urea Nitrogen; Calcium; Uric Acid; Sodium; Potassium; and Chloride. In the area of metabolism, targets may be identified for the treatment of diabetes.

Results:

5 Blood Chemistry: Both the male and female (-/-) mice exhibited increased mean serum alkaline phosphatase levels and decreased mean serum glucose levels when compared with the levels for their gender-matched (+/+) littermates and the historical means. The increased mean serum alkaline phosphatase levels are consistent with the observation of decreased mean bone-mineral density measurements as well as the observed liver abnormalities and chronic hepatitis.

(f) Phenotypic Analysis: CNS/Neurology

10 In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not
15 otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders
20 including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier
25 testing.

Prepulse inhibition of the acoustic startle reflex

Prepulse inhibition of the acoustic startle reflex occurs when a loud 120 decibel (dB) startle-inducing tone is preceded by a softer (prepulse) tone. The PPI paradigm consists of six different trial types (70 dB background noise, 120 dB alone, 74dB + 120 dB - pp4, 78 dB + 120 dB - pp8, 82 dB + 120 dB - pp12, and 90 dB + 120 dB
30 - pp20) each repeated in pseudo random order six times for a total of 36 trials. The max response to the stimulus (V max) is averaged for each trial type. Animals with a 120 dB average value equal to or below 100 are excluded from analysis. The percent that the prepulse inhibits the animal's response to the startle stimulus is calculated and graphed.

Results:

35 Sensorimotor Gating/Attention: The mutant (-/-) mice exhibited a trend towards increased prepulse inhibition of the acoustic startle reflex which is indicative of an enhanced sensorimotor gating/attention.

(g) Bone Metabolism & Body Diagnostics

(1) Tissue Mass & Lean Body Mass Measurements - DEXA

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements: A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

Weight: The female (-/-) mice exhibited decreased mean body weight when compared with that of their gender-matched (+/+) littermates and the historical mean.

(2) Bone Metabolism: Radiology Phenotypic Analysis

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The female (-/-) mice exhibited decreased mean bone mineral content, volumetric bone mineral density, and bone mineral density in total body, femurs, and vertebrae when compared with the levels for their gender-matched (+/+) littermates and the historical means.

5 Micro CT: The male (-/-) mice exhibited decreased mean vertebral trabecular bone volume, number, and connectivity density when compared with the levels for their gender-matched (+/+) littermates and the historical means.

The (-/-) mice analyzed by DEXA and bone micro CT analysis exhibited decreased bone measurements and decreased body mass measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders. The (-/-) mice exhibited a negative bone phenotype with abnormal decreased bone measurements
10 reflective of bone metabolic disorders. The negative bone phenotype indicates that PRO6182 polypeptides or agonists thereof would be useful for maintaining bone homeostasis. In addition, PRO6182 polypeptides would be useful in bone healing or for the treatment of arthritis or osteoporosis, whereas antagonists (or inhibitors) of PRO6182 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with abnormal bone metabolism including arthritis, osteoporosis and osteopenia.
15 The (-/-) mice also showed signs of growth retardation.

66.57. Generation and Analysis of Mice Comprising DNA108722-2743 (UNQ2782) Gene Disruptions

In these knockout experiments, the gene encoding PRO7170 polypeptides (designated as DNA108722-2743) (UNQ2782) was disrupted. The gene specific information for these studies is as follows: the mutated mouse
20 gene corresponds to nucleotide reference: AB098732 Mus musculus mRNA for transmembrane mucin MUC20; protein reference: Q76184 ACCESSION:Q76184 NID: Mus musculus (Mouse). Transmembrane mucin MUC20; the human gene sequence reference: BC029267 Homo sapiens mucin 20, mRNA (cDNA clone MGC:34717 IMAGE:3851952); the human protein sequence corresponds to reference: Q8N307 ACCESSION:Q8N307 NID: Homo sapiens (Human). MUC20 protein.

25 The mouse gene of interest is Muc20 (mucin 20), ortholog of human MUC20. Aliases include MGC31081, FLJ14408, KIAA1359, and cDNA sequence BC026367.

MUC20 is an integral plasma membrane protein expressed primarily in renal proximal tubule epithelial cells. MUC20 is also expressed at moderate levels in placenta, colon, lung, prostate, and liver. MUC20 can interact with the Grb2 docking site on hepatocyte growth factor receptor MET, inhibiting MET signal transduction via the
30 Grb2-Ras pathway. Moreover, MUC20 inhibits hepatocyte growth factor-induced matrix metalloproteinase expression and cell proliferation. These functions suggest that MUC20 plays a regulatory role in HGF signal transduction. MUC20 is upregulated in patients with moderate immunoglobulin A nephropathy and in experimental mouse models of glomerulonephritis, suggesting that MUC20 may play a role in the progression of glomerulonephritis and other renal injuries (Higuchi, Orita, Katsuya et al, Mol Cell Biol 24(17):7456-68 (2004);
35 Higuchi, Orita, Nakanishi et al, J Biol Chem 279(3):1968-79 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for

example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	35	21	74
Expected	18.5	37	18.5	74

Chi-Sq.= 1.69 Significance= 0.42955735 (hom/n)= 0.25 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_146071.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in eye; lung; kidney; and stomach, small intestine, and colon among 13 adult tissue samples tested by RT-PCR.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.57.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA108722-2743 (UNQ2782))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human mucin 20 (MUC20) resulted in immunological abnormalities in (-/-) mice. Although T cell percentages are normal in blood and spleen, there is a reduction in naive T cells in lymph nodes. IgM B cells are increased in bone marrow, but significantly decreased in lymph nodes. In addition, the male mutants exhibited a decreased mean serum insulin level. Male knockout (-/-) mice showed increased total tissue mass and lean body mass. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also

secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

5 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

10 In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and
15 thus ameliorate immune related disease.

The following test was performed:

Flourescence-activated cell-sorting (FACS) Analysis

Procedure:

20 FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T
25 cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCR β APC, CD4 PE, CD8 FITC, pan-NK
30 PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

Tissue Specific FACS-Project: The (-/-) mice exhibited increased IgM+ and CD117+ B cells in bone marrow when compared with those of their (+/+) littermates. Although T cell percentages are normal in blood and spleen,
35 there is a reduction in naive T cells in lymph nodes (especially CD4+). In addition, the (-/-) mice exhibited a higher proportion of dead cells, decreased B cells, and increased CD4 and CD8 T cells in lymph node (although there is a slight decrease of CD8 cells). The (-/-) mice also exhibited an increased CD11b+CD11c- cells (monocytes) in the spleen consistent with the observation of increased monocyte count in the hematological results.

Thus, knocking out the gene which encodes PRO7170 polypeptides causes numerous immunological abnormalities presenting a complex pattern. Essentially there is a pronounced decrease in the B cell population (including pre-B or pro-B cells, immature and mature B cells), as well as a decrease in the T cell population (especially in naive T cells) in the lymph nodes. From these observations, PRO7170 polypeptides or the gene encoding PRO7170 appears to be important for the development of the population of both B and T cells in the lymph nodes. Thus, PRO7170 polypeptides would be beneficial in enhancing or development of both B cell and T cell proliferation.

(c) *Blood Chemistry*

Blood chemistry analysis was performed using the COBAS Integra 400 (mfr: Roche) in its clinical settings for running blood chemistry tests on mice.

Insulin Data:

Test Description: Lexicon Genetics uses the Cobra II Series Auto-Gamma Counting System in its clinical settings for running quantitative Insulin assays on mice.

Results:

Insulin: The male (-/-) mice exhibited a decreased mean serum insulin level when compared with that of their gender-matched (+/+) littermates and the historical mean.

Mutant (-/-) mice deficient in the gene encoding PRO7170 polypeptides show a phenotype marked by low insulin levels which can be indicative of diabetes. Thus, antagonists or inhibitors of PRO7170 polypeptides or its encoding gene would mimic these metabolic related effects. On the other hand, PRO7170 polypeptides or agonists thereof would be useful in the prevention and/or treatment of such metabolic disorders as diabetes.

(d) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

DEXA: Male (-/-) mice exhibited increased mean total tissue mass and lean body mass.

These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that

would be associated with obesity. Thus, PRO7170 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be important in the prevention and/or treatment of obesity or other growth related disorders.

66.58. Generation and Analysis of Mice Comprising DNA108670-2744 (UNQ2783) Gene Disruptions

5 In these knockout experiments, the gene encoding PRO7171 polypeptides (designated as DNA108670-2744) (UNQ2783) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: AA030296 ACCESSION:AA030296 NID:1497436 Mus musculus mi02d10.r1 Soares mouse placenta 4NbMP13.5 14.5 Mus musculus cDNA clone IMAGE:459283 5V; the human gene sequence reference: AY358621 Homo sapiens clone DNA108670 WWLS2783 (UNQ2783); the human
10 protein sequence corresponds to reference: Q6UWV7 ACCESSION:Q6UWV7 NID: Homo sapiens (Human). WWLS2783.

The mouse gene of interest is represented by a partial cDNA (NCBI accession AAO30296), which is orthologous with Homo sapiens clone DNA108670 WWLS2783 (UNQ2783). Aliases include hypothetical protein MGC52498 and PRO7171.

15 UNQ2783 is a putative secreted protein, consisting of 134 amino acids and containing a signal peptide (Clark et al, Genome Res 13(10):2265-70 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for
20 example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	23	32	12	67
25 Expected	16.75	33.5	16.75	67

Chi-Sq.= 3.5 Significance= 0.17377394 (hom/n)= 0.2 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted.

- 30 1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except spleen, kidney, liver, bone, and adipose.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.58.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA108670-2744 (UNQ2783))

35 (a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of a human putative secreted protein (UNQ2783) resulted in the female homozygous mutant mice exhibiting increased total tissue mass and body fat when compared with that of their gender-matched wild-type littermates and the historical mean. The mutant (-/-) mice also exhibited

increased triglyceride levels. Microarray analysis shows overexpression of UNQ2783 in lymphoid tumors. Gene disruption was confirmed by Southern blot.

(b) *Bone Metabolism: Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- 5 · DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

10 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

15 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

20 DEXA: The female (-/-) mice exhibited increased mean total tissue mass, percent total body fat, and total fat mass when compared with the levels for their gender-matched (+/+) littermates and the historical means.

These results demonstrate that knockout mutant mice exhibit abnormal body mass and fat measurements marked by increased mean total tissue mass, lean body mass and increased mean percent total body fat and total fat mass when compared with their gender-matched (+/+) littermates and the historical means.

25 These studies show that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that is associated with obesity. Thus, PRO7171 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be useful in the prevention and/or treatment of lipid storage diseases and/or obesity.

(c) *Diagnostics - Heart Rate/Blood Pressure*

Description

30 Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious systolic blood pressure. The single (-/-) male mouse also exhibited a decreased heart rate (> two standard deviations below historic means).

35 Heart rate is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. Heart rate is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious heart rate.

Results:

Blood Pressure: The (-/-) mice exhibited decreased mean systolic blood pressure when compared with that of their

gender-matched (+/+) littermates and the historical mean.

Heart Rate: The (-/-) mice exhibited an increased mean heart rate when compared with that of their gender-matched (+/+) littermates and the historical mean.

(d) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum triglycerides.

Blood Lipids

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The (-/-) mice exhibited increased mean serum triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means.

As summarized above, the (-/-) mice exhibited notably increased mean serum triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO7171 gene can serve as a model for cardiovascular disease. PRO7171 polypeptides or its encoding gene would be useful in regulating blood lipids such as triglycerides. Thus, PRO7171 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, hypertriglyceridemia, diabetes and/or obesity.

66.59. Generation and Analysis of Mice Comprising DNA119535-2756 (UNQ2973) Gene Disruptions

In these knockout experiments, the gene encoding PRO7436 polypeptides (designated as DNA119535-2756) (UNQ2973) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_177036 Mus musculus RIKEN cDNA C130022P09 gene (C130022P09Rik); protein reference: NP_796010 RIKEN cDNA C130022P09 gene [Mus musculus] gi|26347895|dbj|BAC37596.1| unnamed protein product [Mus musculus]; the human gene sequence reference: NM_020219 Homo sapiens carcinoembryonic antigen-like 1 (CEAL1); the human protein sequence corresponds to reference: Q7Z692 ACCESSION:Q7Z692 NID: Homo sapiens (Human). Carcinoembryonic antigen-like 1 precursor (UNQ2973/PRO7436).

The mouse gene of interest is RIKEN cDNA C130022P09 gene, ortholog of human CEAL1 (carcinoembryonic antigen-like 1). Aliases include DKFZp547N157.

CEAL1 is a putative type I integral membrane protein, containing a signal peptide, an immunoglobulin-like domain, and a transmembrane segment. A second CEAL1 variant lacks the immunoglobulin-like domain. By similarity to other carcinoembryonic antigen (CEA) family members, CEAL1

is likely to be located in the plasma membrane. CEAL1 is broadly expressed and may be overexpressed in subsets of clinically aggressive ovarian cancers. [Scorilas et al., Gene 310:79-89(2003)]

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	46	21	85
Expected	21.25	42.5	21.25	85

Chi-Sq.= 2.38 Significance= 0.30422124 (hom/n)= 0.23 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_177036.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in spinal cord; eye; thymus; spleen; lung; kidney; and stomach, small intestine, and colon among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.59.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA119535-2756 (UNQ2973))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human carcinoembryonic antigen-like 1 (CEAL1) resulted in the homozygous mutant mice exhibiting a significant increase in mean skin fibroblast proliferation rate. The female (-/-) mice also showed decreased body weight and decreased total tissue mass with decreased levels of total body fat and cholesterol. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Adult skin cell proliferation:*

Procedure: Skin cells were isolated from 16 week old animals (2 wild type and 4 homozygotes). These were developed into primary fibroblast cultures and the fibroblast proliferation rates were measured in a strictly controlled protocol. The ability of this assay to detect hyper-proliferative and hypo-proliferative phenotypes has been demonstrated with p53 and Ku80. Proliferation was measured using Brdu incorporation.

Specifically, in these studies the skin fibroblast proliferation assay was used. An increase in the number of cells in a standardized culture was used as a measure of relative proliferative capacity. Primary fibroblasts were established from skin biopsies taken from wild type and mutant mice. Duplicate or triplicate cultures of 0.05 million cells were plated and allowed to grow for six days. At the end of the culture period, the number of cells present in the culture was determined using a electronic particle counter.

Results:

Skin Proliferation: The female (-/-) mice exhibited a notably increased mean skin fibroblast proliferation rate when compared with that of their gender-matched (+/+) littermates and the historical mean.

Thus, homozygous mutant mice demonstrated a hyper-proliferative phenotype. As suggested by these observations, PRO7436 polypeptides or agonists thereof could function as tumor suppressors and would be useful in decreasing abnormal cell proliferation.

(c) *Bone Metabolism & Body Diagnostics*

(1) Tissue Mass & Lean Body Mass Measurements - DEXA

5 *Dexa Analysis - Test Description:*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

10 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

15 Body Measurements: A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

Weight: The female (-/-) mice exhibited decreased mean body weight when compared with that of their gender-matched (+/+) littermates and the historical mean.

(2) Bone Metabolism: Radiology Phenotypic Analysis

20 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

25 *Dexa Analysis - Test Description:*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

30 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

35 Results:

DEXA: The single female (-/-) mice available for analysis exhibited decreased total tissue mass, total fat mass, and percent total body fat when compared with their gender-matched (+/+) littermates and the historical means.

The (-/-) mice analyzed by DEXA exhibited notably decreased total tissue mass and lean body mass as

well as decreased fat measurements when compared with their (+/+) littermates, suggestive of growth retardation in these mutants. This in conjunction with the observations of decreased body weight and length suggest a tissue wasting condition such as cachexia or other growth related disorders. Thus, PRO7436 polypeptides or agonists thereof would be useful in the treatment or prevention of growth disorders including cachexia or other tissue wasting diseases.

5 (d) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides.

10 *Blood Lipids*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The female (-/-) mice exhibited a decreased mean serum cholesterol level when compared with that of their gender-matched (+/+) littermates and the historical mean.

20 As summarized above, the (-/-) mice exhibited notably increased mean serum cholesterol levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO7436 gene can serve as a model for cardiovascular disease. PRO7436 polypeptides or its encoding gene would be useful in regulating blood lipids such as cholesterol.

25 66.60. Generation and Analysis of Mice Comprising DNA108700-2802 (UNQ3077) Gene Disruptions

In these knockout experiments, the gene encoding PRO9912 polypeptides (designated as DNA108700-2802) (UNQ3077) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: XM_137914 PREDICTED: Mus musculus similar to ectonucleotide pyrophosphatase/phosphodiesterase 7; alkaline sphingomyelinase (LOC238011); protein reference: XP_137914
30 ACCESSION:XP_137914 NID: gi 51766567 ref XP_137914.4 similar to ectonucleotide pyrophosphatase/phosphodiesterase 7; alkaline sphingomyelinase [Mus musculus]; the human gene sequence reference: BC041453 ACCESSION:BC041453 NID:27371235 Homo sapiens Homo sapiens, Similar to ectonucleotide pyrophosphatase/phosphodiesterase 5, clone IMAGE:5186743; the human protein sequence corresponds to reference: Q8IUS8 ACCESSION:Q8IUS8 NID: Homo sapiens (Human). Similar to ectonucleotide
35 pyrophosphatase/phosphodiesterase 5 (Fragment).

The mouse gene of interest is "similar to ectonucleotide pyrophosphatase/phosphodiesterase 7; alkaline sphingomyelinase," ortholog of human ENPP7 (ectonucleotide pyrophosphatase/phosphodiesterase 7). Aliases include MGC50179, ALK-SMase, and alkaline sphingomyelinase.

ENPP7 is an ectoenzyme expressed primarily in intestine and liver that catalyzes the hydrolysis of sphingomyelin. The protein consists of a signal peptide, a type I phosphodiesterase/nucleotide pyrophosphatase domain (Pfam accession PF01663), and a hydrophobic region near the C terminus that may loosely anchor the protein to the extracellular surface of the plasma membrane (Duan et al, 2003). Unlike other sphingomyelinases, ENPP7 displays optimal catalytic activity at alkaline pH, trypsin resistance, and specific bile salt dependence. The enzyme is particularly concentrated on the extracellular surface of the microvillar membrane of intestinal epithelial cells and in bile. ENPP7 likely plays a role in dietary sphingomyelin digestion, cholesterol absorption, and colonic tumorigenesis (Duan et al, *J Biol Chem* 278(40):38528 (2003); Wu et al, *Carcinogenesis* 25(8):1327-33 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	22	37	11	70
Expected	17.5	35	17.5	70

Chi-Sq.= 5.18 Significance= 0.075020045 (hom/n)= 0.19 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 3 were targeted (XM_137914.4).

1. Wild-type Expression Panel: Expression of the target gene was detected in brain; thymus; spleen; and stomach, small intestine, and colon among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.60.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA108700-2802 (UNQ3077))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human ectonucleotide pyrophosphatase/phosphodiesterase 7 (ENPP7) resulted in both the male and female heterozygous and homozygous mutant mice exhibiting increased total tissue mass and total body fat when compared with the measurements for their gender-matched wild-type littermates and the historical means. In addition, the knockout (-/-) mice exhibited a decreased anxiety-like response. Gene disruption was confirmed by Southern blot.

(b) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder

without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing. These tests included open field to measure anxiety, activity levels and exploration.

Open field test:

Several targets of known drugs have exhibited phenotypes in the open field test. These include knockouts of the serotonin transporter, the dopamine transporter (Giros et al., Nature. 1996 Feb 15;379(6566):606-12), and the GABA receptor (Homanics et al., Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):4143-8). An automated open-field assay was customized to address changes related to affective state and exploratory patterns related to learning. First, the field (40 X 40 cm) was selected to be relatively large for a mouse, thus designed to pick up changes in locomotor activity associated with exploration. In addition, there were 4 holes in the floor to allow for nose-poking, an activity specifically related to exploration. Several factors were also designed to heighten the affective state associated with this test. The open-field test is the first experimental procedure in which the mice are tested, and the measurements that were taken were the subjects' first experience with the chamber. In addition, the open-field was brightly lit. All these factors will heighten the natural anxiety associated with novel and open spaces. The pattern and extent of exploratory activity, and especially the center-to-total distance traveled ratio, may then be able to discern changes related to susceptibility to anxiety or depression. A large arena (40 cm x 40 cm, VersaMax animal activity monitoring system from AccuScan Instruments) with infrared beams at three different levels was used to record rearing, hole poke, and locomotor activity. The animal was placed in the center and its activity was measured for 20 minutes. Data from this test was analyzed in five, 4-minute intervals. The total distance traveled (cm), vertical movement number (rearing), number of hole pokes, and the center to total distance ratio were recorded.

The propensity for mice to exhibit normal habituation responses to a novel environment is assessed by determining the overall change in their horizontal locomotor activity across the 5 time intervals. This calculated slope of the change in activity over time is determined using normalized, rather than absolute, total distance traveled. The slope is determined from the regression line through the normalized activity at each of the 5 time intervals. Normal habituation is represented by a negative slope value.

Results:

Openfield2: The male (-/-) mice exhibited increased sum time-in-center when compared with the value for their gender-matched (+/+) littermates and the historical mean, suggesting a decreased anxiety-like response in the male mutants.

A notable difference was observed during open field activity testing. The male (-/-) mice exhibited an increased median sum time in the center area when compared with their gender-matched (+/+) littermates, which

is indicative of a decreased anxiety-like response in the mutants. Thus, knockout mice demonstrated a phenotype consistent with depression, generalized anxiety disorders, cognitive disorders, hyperalgesia and sensory disorders and/or bipolar disorders. Thus, PRO9912 polypeptides and agonists thereof would be useful for the treatment or amelioration of the symptoms associated with depressive disorders.

(c) *Bone Metabolism: Radiology Phenotypic Analysis*

- 5 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:
- DEXA for measurement of bone mineral density on femur and vertebra
 - MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

10 *Dexa Analysis - Test Description:*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

- 15 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

20 Results:

DEXA: The male and female (+/-) and (-/-) mice exhibited increased total tissue mass and mean percent total body fat and total fat mass when compared with that of their gender-matched (+/+) littermates and the historical mean.

- 25 These studies show that both homozygous mutant (-/-) mice and heterozygous (+/-) mice exhibit a negative phenotype that is associated with obesity. Thus, PRO9912 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be useful in the prevention and/or treatment of lipid storage diseases, dyslipidemia and/or obesity.

66.61. Generation and Analysis of Mice Comprising DNA119474-2803 (UNQ3079) Gene Disruptions

- 30 In these knockout experiments, the gene encoding PRO9917 polypeptides (designated as DNA119474-2803) (UNQ3079) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_145100 Mus musculus RIKEN cDNA 2700050C12 gene (2700050C12Rik); protein reference: Q9JJ96 ACCESSION:Q9JJ96 NID: Mus musculus (Mouse). Mus musculus brain cDNA, clone MNCb-0671; the human gene sequence reference: NM_144586 Homo sapiens hypothetical protein MGC29643 (MGC29643); the human protein sequence corresponds to reference: Q8N2G4
- 35 ACCESSION:Q8N2G4 NID: Homo sapiens (Human). Hypothetical protein PSEC0181.

The mouse gene of interest is RIKEN cDNA 2700050C12 gene, ortholog of human hypothetical protein MGC29643. Aliases include C530008O16Rik.

MGC29643 is a putative secreted protein, consisting of a signal peptide and an Ly-6 antigen/uPA

receptor-like domain. This domain occurs in urokinase-type plasminogen activator receptor and several glycosylphosphatidylinositol (GPI)-linked cell surface glycoproteins, such as leukocyte antigens. Proteins with this domain can function as cell adhesion or signaling molecules (SMART accession SM00134).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	18	29	16	63
Expected	15.75	31.5	15.75	63

Chi-Sq.= 5.42 Significance= 0.06653681 (hom/n)= 0.23 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_145100.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in brain; spinal cord; eye; thymus; lung; stomach, small intestine, and colon; and heart among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.61.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA119474-2803 (UNQ3079))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human hypothetical protein MGC29643 resulted in the homozygous mutant mice exhibiting a decreased depressive-like response during tail suspension testing and a decreased anxiety-like response during stress-induced hyperthermia testing. In addition, both the male and female mutant mice exhibited increased heart rates when compared with those of their gender-matched wild-type littermates and the historical means. The mutant (-/-) mice also exhibited increased mean serum cholesterol levels and an impaired glucose tolerance. Both male and female (-/-) mice showed increased total tissue mass and total body fat. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides.

Blood Lipids

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the

risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The male (-/-) mice exhibited an increased mean serum cholesterol level when compared with that of their gender-matched (+/+) littermates and the historical mean.

5 As summarized above, the (-/-) mice exhibited notably increased mean serum cholesterol levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO9917 gene can serve as a model for cardiovascular disease. PRO9917 polypeptides or its encoding gene would be useful in regulating blood lipids such as cholesterol. Thus, PRO9917 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, diabetes and/or obesity.

(c) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

20 Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Blood Glucose Levels/Glucose Tolerance Test:

25 The male (-/-) mice exhibited impaired glucose tolerance when placed on a high fat diet compared with their gender-matched (+/+) littermates and the historical means.

30 These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose homeostasis, and therefore PRO9917 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

(d) *Diagnostics - Heart Rate*

Description

35 Heart rate is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. Heart rate is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious heart rate.

Results:

Heart Rate: The (-/-) mice exhibited increased mean heart rates (~2 SD above the mean) when compared with those of their gender-matched (+/+) littermates and the historical means.

(e) Phenotypic Analysis: CNS/Neurology

In the area of neurology, analysis focused herein on identifying *in vivo* validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Functional Observational Battery (FOB) Test - Tail Suspension Testing:

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general, short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Tail Suspension Testing:

The tail suspension test is a procedure that has been developed as a model for depressive-like behavior in rodents. In this particular setup, a mouse is suspended by its tail for 6 minutes, and in response the mouse will struggle to escape from this position. After a certain period of time the struggling of the mouse decreases and this is interpreted as a type of learned helplessness paradigm. Animals with invalid data (i.e. climbed their tail during the testing period) are excluded from analysis.

Results:

Tail Suspension2: The (-/-) mice exhibited decreased immobility time when compared with the value for their (+/+) littermates and the historical mean, which is indicative of a decreased depressive-like response in the mutants. Thus, antagonists (inhibitors) of PRO9917 would be expected to mimic this phenotype.

Functional Observational Battery (FOB) Test - Stress-induced Hyperthermia:

The FOB is a series of situations applied to the animal to determine gross sensory and motor deficits. A subset of tests from the Irwin neurological screen that evaluates gross neurological function is used. In general,

short-duration, tactile, olfactory, and visual stimuli are applied to the animal to determine their ability to detect and respond normally. These simple tests take approximately 10 minutes and the mouse is returned to its home cage at the end of testing.

Results:

5 Stress-Induced Hyperthermia: The (-/-) mice exhibited resistance to stress-induced hyperthermia when compared with the value for their gender-matched (+/+) littermates and the historical mean, suggesting a decreased anxiety-like response in the mutants. Thus antagonists or inhibitors of PRO9917 polypeptides would be expected to mimic this phenotype and would be useful in the treatment of anxiety related disorders.

(f) *Bone Metabolism: Radiology Phenotypic Analysis*

10 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:
 · DEXA for measurement of bone mineral density on femur and vertebra
 · MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

15 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

20 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Results:

25 DEXA: The (-/-) mice exhibited increased total tissue mass and mean percent total body fat and total fat mass when compared with that of their gender-matched (+/+) littermates and the historical mean.

30 These studies show that mutant (-/-) mice exhibit a negative phenotype that is associated with obesity. Thus, PRO9917 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be useful in the prevention and/or treatment of lipid storage diseases, dyslipidemia and/or obesity.

66.62. Generation and Analysis of Mice Comprising DNA226874 (UNQ5291) Gene Disruptions

35 In these knockout experiments, the gene encoding PRO37337 polypeptides (designated as DNA226874) (UNQ5291) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_010128 Mus musculus epithelial membrane protein 1 (Emp1); protein reference: P47801 ACCESSION:P47801 NID: Mus musculus (Mouse). Epithelial membrane protein-1 (EMP-1) (Tumor-associated membrane protein); the human gene sequence reference: NM_001423 Homo sapiens epithelial membrane protein 1 (EMP1); the human protein sequence corresponds to reference: P54849 ACCESSION:P54849 NID: Homo sapiens (Human). Epithelial membrane protein-1 (EMP-1) (Tumor-associated membrane protein)

(CL-20) (B4B protein).

The mouse gene of interest is Emp1 (epithelial membrane protein 1), ortholog of human EMP1. Aliases include tumor-associated membrane protein, TMP, B4B protein, and CL-20.

EMP1 is a putative integral plasma membrane glycoprotein, consisting of four transmembrane segments within a single PMP22 family domain (Lobsiger et al, Genomics **36**(3):379-87 (1996); Marvin et al, J Biol Chem **270**(48):28910-6 (1995); Ruegg et al, J Immunol **157**(1):72-80 (1996)). EMP1 is structurally similar to claudins, which function as components of tight junctions, and voltage-dependent calcium channel gamma subunits, which function as regulatory subunits (InterPro accession IPR004031). EMP1 is expressed primarily in neurons during development (Wulf and Suter, Brain Res Dev Brain Res **116**(2):169-80 (1999)) but is also expressed in several other tissues, including tumors (Ben-Porath and Benvenisty, Gene **183**(1-2):69-75 (1996)), squamous-differentiated bronchial epithelial cells (Chen et al, Genomics **41**(1):40-8 (1997)), and a subpopulation of immature B cells (Ruegg et al, J Immunol **157**(1):72-80 (1996)). EMP1 may play a role in processes such as cell proliferation, development, differentiation, and cell death (Ruegg et al, J Immunol **157**(1):72-80 (1996); Wang et al, World J Gastroenterol **9**(3):392-8 (2003); Wulf and Suter, Brain Res Dev Brain Res **116**(2):169-80 (1999)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	10	41	13	64
Expected	16	32	16	64

Chi-Sq.= 1.35 Significance= 0.5091564 (hom/n)= 0.23 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_010128.3).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.62.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA226874 (UNQ5291))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human epithelial membrane protein 1 (EMP1) resulted in the mutant (-/-) mice exhibiting increased bone-mineral density measurements. Both the male and female (-/-) mice exhibited increased total tissue mass and total body fat. The female (-/-) mice also exhibited decreased mean systolic blood pressure when compared with their gender-matched (+/+) littermates and the historical mean. Embryonic expression showed a strong signal in the vasculature. Gene disruption was confirmed by Southern blot.

(b) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

DEXA: The (-/-) mice exhibited increased total tissue mass and total body fat. In addition, the male (-/-) mice exhibited increased mean volumetric bone mineral density and bone mineral density in total body and femur when compared with their gender-matched (+/+) littermates and the historical means.

Micro CT: The male (-/-) mice exhibited increased mean femoral mid-shaft cross-sectional area when compared with their gender-matched (+/+) littermates and the historical mean.

These results demonstrate that knockout mutant mice exhibit abnormal bone metabolism with increased bone measurements similar to osteopetrosis characterized by increase in bone mass. The knockout (-/-) mice also exhibited signs of an obesity phenotype. Thus, it appears that PRO37337 polypeptides or agonists thereof would be useful in maintaining bone homeostasis and for bone remodeling by balancing osteoclast and osteoblast activity. In addition, antagonists or inhibitors of PRO37337 polypeptides or its encoding gene would be useful in bone healing or for the treatment of other bone related abnormalities associated with increased bone mineralization. PRO37337 polypeptides or agonists thereof would also be useful for maintaining normal lipid metabolism.

66.63. Generation and Analysis of Mice Comprising DNA227033 (UNQ5407) Gene Disruptions

In these knockout experiments, the gene encoding PRO37496 polypeptides (designated as DNA227033) (UNQ5407) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_010762 Mus musculus myelin and lymphocyte protein, T-cell differentiation protein (Mal); protein reference: O09198 ACCESSION:O09198 NID: Mus musculus (Mouse).
 5 Myelin and lymphocyte protein (T-lymphocyte maturation-associated protein); the human gene sequence reference: NM_002371 ACCESSION:NM_002371 NID: gi 12408666 ref NM_002371.2 Homo sapiens mal, T-cell differentiation protein (MAL), transcript variant a; the human protein sequence corresponds to reference: P21145 ACCESSION:P21145 NID: Homo sapiens (Human). Myelin and lymphocyte protein (T-lymphocyte maturation-associated protein).

10 The mouse gene of interest is Mal (myelin and lymphocyte protein, T-cell differentiation protein), ortholog of human MAL (mal, T-cell differentiation protein). Aliases include MPV17, VIP17, myelin and lymphocyte protein, and T-cell differentiation protein MAL.

MAL is a lipophilic integral membrane protein, consisting of four transmembrane segments contained within a MARVEL (membrane-associated) domain (Pfam accession PF01284). MAL is found in
 15 glycolipid-enriched microdomains of epithelial cells, mature T-cells, and myelin-forming cells. Moreover, MAL has been detected in several subcellular locations, including endoplasmic reticulum, Golgi apparatus, large vesicles, and plasma membrane. The function of MAL is not clearly known; however, it may play a role in polarized glycolipid and protein transport, vesicle formation, and myelination (Marazuela and Alonso, Histol Histopathol 19(3):925-33 (2004); Puertollano et al, J Biol Chem 272(29):18311-5 (1997); Magyar et al, Gene 189(2):269-75 (1997); Erne et al, J Neurochem 82(3):550-62 (2002); Schaeren-Wiemers et al, J Cell Biol 166(5):731-42 (2004); Saravanan et al, Neurobiol Dis 16(2):396-406 (2004); Frank et al, J Neurochem 73(2):587-97 (1999); Frank, Prog Neurobiol 60(6):531-44 (2000)).

Schaeren-Wiemers and colleagues (2004) investigated the physiological role of MAL using knockout mice. They showed that myelin formation and paranode-axon interface structure were abnormal in MAL-deficient
 25 mice but not in wild-type mice. The authors concluded that MAL is critical for paranode formation in the central nervous system. They proposed that MAL likely controls trafficking or sorting of various membrane components in oligodendrocytes.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are
 30 intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
35 Observed	21	37	18	76
Expected	19	38	19	76

Chi-Sq.= 2.09 Significance= 0.35169184 (hom/n)= 0.24 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_010762.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except thymus, lung, liver, skeletal muscle, and bone.
2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

5

66.63.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA227033 (UNQ5407))

(a) *OVERALL PHENOTYPIC SUMMARY:*

10 Mutation of the gene encoding the ortholog of human mal, T-cell differentiation protein (MAL) resulted in the homozygous mutant mice exhibiting a decreased mean percentage of CD8 cells in the peripheral blood and decreased naive CD4 and CD8 T cells in the lymph nodes when compared with that of their wild-type littermates and the historical mean. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Immunology Phenotypic Analysis*

15 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

20 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

25 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic
30 T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

35 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

Flourescence-activated cell-sorting (FACS) Analysis/Tissue Specific FACS

Procedure:

FACS analysis of immune cell composition from peripheral blood was performed including CD4, CD8 and T cell receptor to evaluate T lymphocytes, CD19 for B lymphocytes, CD45 as a leukocyte marker and pan NK for natural killer cells. The FACS analysis was carried out on 2 wild type and 6 homozygous mice and included cells derived from thymus, spleen, bone marrow and lymph node.

In these studies, analyzed cells were isolated from thymus, peripheral blood, spleen, bone marrow and lymph nodes. Flow cytometry was designed to determine the relative proportions of CD4 and CD8 positive T cells, B cells, NK cells and monocytes in the mononuclear cell population. A Becton-Dickinson FACSCalibur 3-laser FACS machine was used to assess immune status. For Phenotypic Assays and Screening, this machine records CD4+/CD8-, CD8+/CD4-, NK, B cell and monocyte numbers in addition to the CD4+/CD8+ ratio.

The mononuclear cell profile was derived by staining a single sample of lysed peripheral blood from each mouse with a panel of six lineage-specific antibodies: CD45 PerCP, anti-TCRb APC, CD4 PE, CD8 FITC, pan-NK PE, and CD19 FITC. The two FITC and PE labeled antibodies stain mutually exclusive cell types. The samples were analyzed using a Becton Dickinson FACSCalibur flow cytometer with CellQuest software.

Results:

FACS3: The (-/-) mice exhibited an altered distribution of leukocyte subsets in the peripheral blood, characterized by a decreased mean percentage of CD8 cells and reduced percentages of naive CD4 and CD8 T cells in lymph nodes when compared with that of their (+/+) littermates.

By knocking out the gene encoding PRO37496 polypeptides, the mutant (-/-) mice exhibited a decreased mean percentage of CD8 cells and CD4 naive T cells. CD8 proteins are the co-receptor molecules which bind/recognize the MHC Class I molecules for cooperation with the T cell receptor in antigen recognition. Thus, PRO37496 polypeptides or agonists thereof would stimulate the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, antagonists or inhibitors of PRO37496 polypeptides would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

In addition, the (-/-) mice exhibited decreased mean percentages of naive CD4 cells in the cell population when compared with their (+/+) littermates and the historical means. Thus, knocking out the gene which encodes PRO37496 polypeptides causes a decrease in the T cell population. From these observations, PRO37496 polypeptides or the gene encoding PRO37496 appears to act as a regulator of T cell proliferation. Thus, PRO37496 polypeptides would be beneficial in enhancing T cell proliferation.

66.64. Generation and Analysis of Mice Comprising DNA145841-2868 (UNQ5827) Gene Disruptions

In these knockout experiments, the gene encoding PRO19646 polypeptides (designated as DNA145841-2868)(UNQ5827) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_172898 Mus musculus kin of IRRE like 2 (Drosophila) (Kirrel2); protein reference: Q7TSU7 ACCESSION:Q7TSU7 NID: Mus musculus (Mouse). Kin of IRRE-like 2; the human gene sequence reference: NM_199180 Homo sapiens kin of IRRE like 2 (Drosophila) (KIRREL2), transcript variant 3; the human protein sequence corresponds to reference: Q6UWL6 ACCESSION:Q6UWL6 NID: Homo sapiens (Human). Kin of IRRE-like protein 2 precursor (Kin of irregular chiasm-like protein 2) (Nephrin-like protein 3) (UNQ5827/PRO19646).

The mouse gene of interest is Kirrel2 (kin of IRRE like 2 [Drosophila]), ortholog of human KIRREL2. Aliases include NLG1, NEPH3, FILTRIN, MGC15718, DKFZP564A1164, C330019F22Rik, kin of irregular chiasm-like 2, X kin of IRRE like 2 (Drosophila), nephrin-like 3, and nephrin-like gene 1.

KIRREL2 is a type I integral plasma membrane protein that likely functions as a cell adhesion molecule. The protein contains a signal peptide, 5 Ig-like domains, a transmembrane segment, and a cytoplasmic C-terminus containing nine amino acids conserved in family members KIRREL and KIRREL3. The C-terminal domain of KIRREL2, like those of KIRREL and KIRREL3, is capable of interacting with podocin, a component of a structure (slit diaphragm) that functions as a glomerular filtration barrier. KIRREL2 is expressed in many different tissues but appears to be primarily expressed in pancreatic islet beta cells and in lymph nodes. Moreover, expression of KIRREL2 negatively correlates with T-cell invasion of pancreatic islets and development of diabetes in nonobese diabetic (NOD) mice. KIRREL2 may be involved in physiological processes such as glomerular filtration, pancreatic beta cell function, and immunity (Ihalmo et al, *Biochem Biophys Res Commun* 300(2):364-70 (2003); Sellin et al, *FASEB J* 17(1):115-7 (2003); Sun et al, *Genomics* 82(2):130-42 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	14	31	13	58
Expected	14.5	29	14.5	58

Chi-Sq.= 0.74 Significance= 0.6907343 (hom/n)= 0.22 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 3 were targeted (NCBI accession NM_172898.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in brain; spinal cord; eye; and stomach, small intestine, and colon among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.64.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA145841-2868 (UNQ5827))(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human kin of IRRE like 2 (*Drosophila*) (KIRREL2) resulted in the mutant (-/-) mice exhibiting decreased mean body weight and length. In addition, the male (-/-) mice showed degeneration of the seminiferous tubules. Gene disruption was confirmed by Southern blot.

5 (b) *Pathology*

Microscopic: Both of the male (-/-) mice analyzed exhibited vacuolar degeneration of the seminiferous tubules. One (-/-) mouse (M-173) also exhibited a microvesicular fatty change in the centrilobular portion of the liver.

Gene Expression: Expression of the target gene was not detected in the panel of tissues by immunohistochemical analysis.

10 (c) *Bone Metabolism & Body Diagnostics*(1) *Tissue Mass & Lean Body Mass Measurements - Dexa**Dexa Analysis - Test Description:*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

15 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

20 *Body Measurements (Body Length & Weight):*

Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

25 Body Weight and Length: The male (-/-) mice exhibited decreased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean. Thus, the mutant (-/-) mice exhibited a phenotype that could be associated with growth retardation. PRO19646 polypeptides or agonists thereof would be useful in promoting normal growth whereas inhibitors or antagonists of PRO19646 polypeptides would mimic this negative phenotype.

30 66.65. Generation and Analysis of Mice Comprising DNA188342 (UNQ5893) Gene Disruptions

In these knockout experiments, the gene encoding PRO21718 polypeptides (designated as DNA188342) (UNQ5893) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: BC024587 ACCESSION:BC024587 NID:19354042 *Mus musculus* *Mus musculus*, Similar to RIKEN cDNA 5830408F06 gene, clone MGC:37716 IMAGE:5066283; protein reference: 35 Q9D3G2 ACCESSION:Q9D3G2 NID: *Mus musculus* (Mouse). 5830408F06Rik protein; the human gene sequence reference: NM_020125 ACCESSION:NM_020125 NID: gi 9910341 ref NM_020125.1 *Homo sapiens* B lymphocyte activator macrophage expressed (BLAME); the human protein sequence corresponds to reference: Q9P0V8 ACCESSION:Q9P0V8 NID: *Homo sapiens* (Human). BCM-like membrane protein (Hypothetical protein

FLJ90188).

The mouse gene of interest is Slamf8 (SLAM family member 8), ortholog of human SLAMF8. Aliases include Blame, SBBI42, 5830408F06Rik, B lymphocyte activator macrophage expressed, and BCM-like membrane protein precursor.

5 SLAMF8 is a type I plasma membrane protein that likely functions as a receptor or B-cell co-receptor. SLAMF8 is expressed in several lymphoid tissues, including lymph node, spleen, thymus, and bone marrow, and in interferon-gamma-activated peripheral blood mononuclear cells, adherence-activated monocytes and dendritic cell subsets. SLAMF8 likely plays a role in B-cell lineage commitment or B-cell receptor signaling (Kingsbury et al, *J Immunol* 166(9):5675-80 (2001)).

10 Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	28	41	20	89
Expected	22.25	44.5	22.25	89

Chi-Sq.= 2.35 Significance= 0.308819 (hom/n)= 0.26 Avg. Litter Size= 10

Mutation Information

20 Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession BC024587.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except skeletal muscle, bone, and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

25

66.65.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA188342 (UNQ5893))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human SLAM family member 8 (SLAMF8) resulted in the mutant (-/-) mice exhibiting an impaired glucose tolerance. Gene disruption was confirmed by Southern blot.

30

(b) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

35

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose

tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Blood Glucose Levels/Glucose Tolerance Test:

5 The (-/-) mice exhibited impaired glucose tolerance when placed on a high fat diet and when compared with their gender-matched (+/+) littermates and the historical means.

These studies indicated that (-/-) mice exhibit a decreased or impaired glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mutant mice exhibited the phenotypic pattern of an impaired glucose
10 homeostasis, and therefor PRO21718 polypeptides (or agonists thereof) or its encoding gene would be useful in the treatment of conditions associated with an impaired glucose homeostasis and/or various cardiovascular diseases, including diabetes.

66.66. Generation and Analysis of Mice Comprising DNA149911-2885 (UNQ5926) Gene Disruptions

15 In these knockout experiments, the gene encoding PRO19820 polypeptides (designated as DNA149911-2885) (UNQ5926) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_026516 ACCESSION:NM_026516 NID: gi 21312655 ref NM_026516.1 Mus musculus RIKEN cDNA 2810417M05 gene (2810417M05Rik); protein reference: Q9CZ16 ACCESSION:Q9CZ16 NID: Mus musculus (Mouse). 2810417M05Rik protein; the human gene sequence
20 reference: NM_152390 ACCESSION:NM_152390 NID: gi 22748834 ref NM_152390.1 Homo sapiens hypothetical protein MGC33926 (MGC33926); the human protein sequence corresponds to reference: Q8NBL3 ACCESSION:Q8NBL3 NID: Homo sapiens (Human). Hypothetical protein PLACE1004322.

The mouse gene of interest is RIKEN cDNA 2810417M05 gene, ortholog of human hypothetical protein MGC33926.

25 Hypothetical protein MGC33926 is a 297-amino acid polypeptide, containing a signal peptide, three potential transmembrane segments, and a potential glycosylphosphatidylinositol (GPI) anchor site near the C-terminus. The predicted function and cell location of this hypothetical protein is ambiguous. Bioinformatic analyses suggest that the transmembrane domains are similar to those of claudins, integral plasma membrane proteins that typically function as components of tight junctions (TrEMBL accession Q8NBL3; InterPro accession
30 IPR006187). Other bioinformatic analyses suggest that the human protein is tethered to the extracellular surface of the plasma membrane by a GPI anchor.

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for
35 example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	14	40	19	73
Expected	18.25	36.5	18.25	73

Chi-Sq.= 2.42 Significance= 0.29819727 (hom/n)= 0.29 Avg. Litter Size= 8

Mutation Information

5 Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_026516.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in the 13 adult tissue samples tested by RT-PCR, except skeletal muscle; bone; stomach, small intestine, and colon; and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

10

66.66.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA149911-2885 (UNQ5926))

(a) *OVERALL PHENOTYPIC SUMMARY:*

15 Mutation of the gene encoding the ortholog of a human hypothetical protein (MGC33926) resulted in the male homozygous mutant mice exhibiting an increased anxiety-like response during stress-induced hyperthermia testing when compared with the level for their gender-matched wild-type littermates and the historical mean. Defecation was absent in 3 of 8 (-/-) mutant mice. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Phenotypic Analysis: CNS/Neurology*

20 In the area of neurology, analysis focused herein on identifying in vivo validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

30

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

35

Results:

Stress-Induced Hyperthermia: The male (-/-) mice exhibited increased sensitivity to stress-induced hyperthermia when compared with the level for their gender-matched (+/+) littermates and the historical mean, suggesting an increased anxiety-like response in the mutants.

In summary, the functional observational testing revealed a phenotype associated with increased anxiety which could be associated with mild to moderate anxiety, anxiety due to a general medical condition, and/or bipolar disorders; hyperactivity; sensory disorders; obsessive-compulsive disorders, schizophrenia or a paranoid personality. Thus, PRO19820 polypeptides, or agonists thereof would be useful in the treatment of such neurological disorders.

5

66.67. Generation and Analysis of Mice Comprising DNA168028-2956 (UNQ6098) Gene Disruptions

In these knockout experiments, the gene encoding PRO21201 polypeptides (designated as DNA168028-2956) (UNQ6098) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_172416 ACCESSION:NM_172416 NID: gi 29293830 ref
10 NM_172416.2 Mus musculus grey lethal osteopetrosis (Gl-pending); protein reference: Q8BGT0 ACCESSION:Q8BGT0 NID: Mus musculus (Mouse). Osteopetrosis associated transmembrane protein 1 precursor (Gray- lethal protein); the human gene sequence reference: NM_014028 ACCESSION:NM_014028 NID: gi 30025025 ref NM_014028.2 Homo sapiens grey-lethal osteopetrosis (GL); the human protein sequence corresponds to reference: Q86WC4 ACCESSION:Q86WC4 NID: Homo sapiens (Human). Osteopetrosis
15 associated transmembrane protein 1 precursor (HSPC019) (UNQ6098/PRO21201).

The mouse gene of interest is Ostm1 (osteopetrosis associated transmembrane protein 1), ortholog of human OSTM1. Aliases include GL, GIPN, HSPC019, 1200002H13Rik, grey-lethal, grey-lethal osteopetrosis, grey lethal osteopetrosis, and GAIP-interacting protein N terminus.

OSTM1 is a putative E3 ubiquitin ligase expressed in osteoblasts, melanocytes, kidney, brain, thymus,
20 spleen, and several other tissues. The protein is located in the cytosol and in cytoplasmic membrane compartments, particularly the basolateral membrane of the renal distal tubule. OSTM1 catalyzes the ubiquitination of the G protein alpha subunit i3 (GNAI3); thus, the protein likely regulates G protein-mediated signal transduction by degradation via the proteasome pathway. OSTM1 is also required for osteoclast and melanocyte maturation and function. Loss-of-function mutations in the OSTM1 gene cause osteopetrosis in humans and mice and coat color
25 defect in mice (Chalhoub et al, Nat Med 9(4):395-406 (2003); Fischer et al, Proc Natl Acad Sci U S A 100(14):8270-5 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for
30 example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	26	39	26	91
Expected	22.75	45.5	22.75	91

35

Chi-Sq.= 3.18 Significance= 0.0392561 (hom/n)= 0.31 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exon 1 was targeted (NCBI accession NM_172416.2).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR, except bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

5 66.67.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA168028-2956 (UNQ6098))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human osteopetrosis associated transmembrane protein 1 (OSTM1) resulted in the homozygous mutant mice being notably smaller than their wild-type littermates. The knockout (-/-) mice exhibited a failure to thrive, showed very reduced mean body weight, had a grey coat color, and possessed no teeth. Microscopic analysis revealed retinal degeneration, neuronal necrosis, and osteopetrosis in the homozygous mutants. The heterozygous mice exhibited an increased mean serum IL-6 response to LPS challenge when compared with their wild-type littermates and the historical mean. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Pathology*

15 Microscopic: The (-/-) mice exhibited diffuse marked osteopetrosis, diffuse moderate retinal degeneration, and multifocal mild neuronal necrosis. The medullary cavities of all long bones, vertebrae, and sternbra were filled with woven trabecular bone. Osteoclasts were increased in number and frequently had large vesicular nuclei (activated). In some areas, there were degenerating and necrotic osteoclasts. Osteoblasts were also numerous, although they tended to be elongated and fibroblastic. Bones in the skull, nasal trabeculae, and epiphyses of long bones contained abundant loosely woven bone and trabeculae. Molar teeth failed to erupt through the bony matrix and there were disorganized dysplastic odontogenic tissues at the base of the impacted incisor teeth. The retinal degeneration affected the receptor and external nuclear layers. Numerous macrophages were present in the photoreceptor layer. In the cerebral cortex, there was laminar degeneration and necrosis/apoptosis of layer IV/V neurons. Similarly affected neurons were also present in the hippocampus and dentate gyrus. All of the mutant mice organs were small, but most were proportional to the weight of the mice (1/2 to 1/3 the weight of the (+/+) littermates). However, the thymus tended to be smaller (about 1/10th the weight for (+/+) littermates).

25 Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) *Bone Metabolism & Body Diagnostics*

(1) *Tissue Mass & Lean Body Mass Measurements - DEXA*

30 *DEXA Analysis - Test Description:*

Procedure: A cohort of wild type, heterozygotes and homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body length and weight was performed at approximately 16 weeks of age.

Results:

Obvious General Observations: The (-/-) mice were small with a grey coat color and no teeth. The mutants either died or were sacrificed due to their failure to thrive.

- 5 Weight: The (-/-) mice exhibited notably decreased mean body weight when compared with their gender-matched (+/+) littermates and the historical means at the 2- and 4-week measurements. Length data was not collected for the (-/-) mice but in the gross photo the (-/-) mice appeared to be shorter than the (+/+) sibling.

- 10 Thus, the mutant (-/-) mice exhibited a phenotype that could be associated with reduced viability and growth retardation. The absence of teeth is consistent with the pathological observations that the molar teeth failed to erupt through the bony matrix. Thus, PRO21201 polypeptides or agonists thereof appear to be essential for normal growth and development, whereas inhibitors or antagonists of PRO21201 polypeptides would mimic this negative phenotype.

(d) Immunology Phenotypic Analysis

- 15 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

- 20 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

- 25 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

- 30 In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

- 35 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the

area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Acute Phase Response:

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sub-lethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNF α , MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

The (+/-) mice exhibited increased mean serum IL-6 responses to LPS challenge when compared with their (+/+) littermates and the historical means.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO21201 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (IL-6 production) when challenged with the LPS endotoxin indicating a pro-inflammatory response. IL-6 contribute to the later stages of B cell activation. In addition, IL-6 plays a critical role in inducing the acute phase response and systemic inflammation.

66.68. Generation and Analysis of Mice Comprising DNA154095-2998 (UNQ6115) Gene Disruptions

In these knockout experiments, the gene encoding PRO20026 polypeptides (designated as DNA154095-2998) (UNQ6115) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_134437 ACCESSION:NM_134437 NID: gi 24025661 ref NM_134437.1 Mus musculus similar expression to Fgf genes (Sef-pending); protein reference: Q8JZL1 ACCESSION:Q8JZL1 NID: Mus musculus (Mouse). Transmembrane protein (Interleukin 17 receptor-like protein long form); the human gene sequence reference: AF494208 Homo sapiens interleukin 17 receptor-like protein long form (IL17RLM); the human protein sequence corresponds to reference: Q8NFM7 ACCESSION:Q8NFM7 NID: Homo sapiens (Human). Interleukin 17 receptor-like protein long form.

The mouse gene of interest is Il17rd (interleukin 17 receptor D), ortholog of human IL17RD. Aliases include Sef, Sef-S, similar expression to Fgf genes, IL17RLM, FLJ35755, DKFZp434N1928, and similar expression to FGF protein.

IL17RD is a type I plasma membrane protein that likely functions as a receptor or signaling molecule involved in feedback inhibition of fibroblast growth factor (FGF) signaling and in activation of pathways regulating apoptosis. A shorter cytosolic isoform of IL17RD generated by alternative splicing also inhibits FGF signaling.

IL17RD inhibits FGF signaling by blocking FGF receptor tyrosine phosphorylation and RAS/ERK MAP kinase pathway. IL17RD stimulates apoptosis by activating TAK1/c-Jun N-terminal kinase pathway. IL17RD is expressed in vascular endothelial cells, in highly vascularized tissues, such as kidney, colon, skeletal muscle, heart, and small intestine, and in ductal epithelial cells of kidney, salivary glands, and seminal vesicles. Expression of the cytosolic form of IL17RD is apparently more limited. IL17RD likely plays a role in processes such as cell proliferation, cell migration, differentiation, apoptosis, and angiogenesis (Yang et al, *J Biol Chem* 279(37):38099-102 (2004); Torii et al, *Dev Cell* 7(1):33-44 (2004); Preger et al, *Proc Natl Acad Sci U S A* 101(5):1229-34 (2004); Xiong et al, *J Biol Chem* 278(50):50273-82 (2003); Yang et al, *J Biol Chem* 278(35):33232-8 (2003); Kovalenko et al, *J Biol Chem* 278(16):14087-91 (2003); Furthauer et al, *Nat Cell Biol* 4(2):170-4 (2002); Tsang et al, *Nat Cell Biol* 4(2):165-9 (2002)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	16	25	14	55
Expected	13.75	27.5	13.75	55

Chi-Sq.= 0.2 Significance= 0.9048374 (hom/n)= 0.25 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Coding exon 4 was targeted (NCBI accession NM_134437.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except thymus; liver; stomach, small intestine, and colon; and adipose.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.68.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA154095-2998 (UNQ6115))

(a) *OVERALL PHENOTYPIC SUMMARY:*

Mutation of the gene encoding the ortholog of human interleukin 17 receptor D (IL17RD) resulted in the male homozygous mutant mice being larger than their gender-matched wild-type littermates, exhibiting increased body weight and length, increased total tissue mass, and increased lean body mass. The male (-/-) mice showed increased total fat mass with a similar trend in serum triglyceride levels. The male (-/-) mice also showed decreased blood pressure and an atrophic testes. The male mutants exhibited enhanced glucose tolerance. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) *Cardiology - Blood Pressure*

Test Description: Systolic blood pressure is measured via a noninvasive tail-cuff method for four days on the Visitech BP-2000 Blood Pressure Analysis System. The blood pressure is measured ten times each day for four days. The four days are then averaged to obtain a mouse's conscious systolic blood pressure.

Results

Blood Pressure: The male (-/-) mice exhibited decreased blood pressure when compared with that of the (+/+) littermates and the historical mean.

(c) *Phenotypic Analysis: Metabolism -Blood Chemistry/Glucose Tolerance*

In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes blood glucose measurements. The COBAS Integra 400 (mfr: Roche) was used for running blood chemistry tests on the mice. In the area of metabolism, targets may be identified for the treatment of diabetes. Blood chemistry phenotypic analysis includes glucose tolerance tests to measure insulin sensitivity and changes in glucose metabolism. Abnormal glucose tolerance test results may indicate but may not be limited to the following disorders or conditions: Diabetes Type 1 and Type 2, Syndrome X, various cardiovascular diseases and/or obesity.

Procedure: A cohort of 2 wild type and 4 homozygous mice were used in this assay. The glucose tolerance test is the standard for defining impaired glucose homeostasis in mammals. Glucose tolerance tests were performed using a Lifescan glucometer. Animals were injected IP at 2g/kg with D-glucose delivered as a 20% solution and blood glucose levels were measured at 0, 30, 60 and 90 minutes after injection.

Results:

Oral Glucose Tolerance: The male (-/-) mice exhibited enhanced glucose tolerance when compared with that of their gender-matched (+/+) littermates and the historical means.

In these studies the mutant (-/-) mice showed an increased or enhanced glucose tolerance in the presence of normal fasting glucose at all 3 intervals tested when compared with their gender-matched (+/+) littermates and the historical means. Thus, knockout mice exhibited an increased insulin sensitivity or the opposite phenotypic pattern of an impaired glucose homeostasis, and as such antagonists (inhibitors) to PRO20026 polypeptides or its encoding gene would be useful in the treatment of an impaired glucose homeostasis.

(d) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum triglycerides.

Blood Lipids

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: The (-/-) mice exhibited increased mean serum triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means.

As summarized above, the (-/-) mice exhibited notably increased mean serum triglyceride levels when

compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO20026 gene can serve as a model for cardiovascular disease. PRO20026 polypeptides or its encoding gene would be useful in regulating blood lipids such as triglycerides. Thus, PRO20026 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, hypertriglyceridemia, diabetes and/or obesity.

5 (e) *Bone Metabolism & Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
 - MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both
- 10 trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

15

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

20

CAT-Scan Protocol:

Mice were injected with a CT contrast agent, Omnipaque 300 (Nycomed Amershan, 300 mg of iodine per ml, 0.25ml per animal, or 2.50-3.75 g iodine/kg of body weight) intraperitoneally. After resting in the cage for ~ 10 minutes, the mouse was then sedated by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight). A CAT-scan was performed using a MicroCAT scanner (ImTek, Inc.) with the anesthetized animal lying prone on the test bed. Three dimensional images were reconstructed by the Feldkamp algorithm in a cluster of workstations using an ImTek 3D RECON software.

25

Results:

DEXA: The male (-/-) mice exhibited increased mean total tissue mass, lean body mass, and total fat mass when compared with that of their gender-matched (+/+) littermates and the historical means.

30

These studies suggest that mutant (-/-) non-human transgenic animals exhibit a negative phenotype that would be associated with obesity. Thus, PRO20026 polypeptides or agonists thereof are essential for normal growth and metabolic processes and especially would be important in the prevention and/or treatment of obesity.

CAT Scan: The two male (-/-) mice analyzed (M-75 and M-100) exhibited atrophic left testes.

35

66.69. Generation and Analysis of Mice Comprising DNA166819-P1381R1C1P1 (UNQ6129) Gene Disruptions

In these knockout experiments, the gene encoding PRO20110 polypeptides (designated as DNA166819-

1381R1C1P1) (UNQ6129) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_145856 ACCESSION:NM_145856 NID: gi 22003915 ref NM_145856.1 Mus musculus interleukin 17F (IL-17F); protein reference: Q8K4C3 ACCESSION:Q8K4C3 NID: Mus musculus (Mouse). IL-17F; the human gene sequence reference: NM_052872 Homo sapiens interleukin 17F (IL17F), transcript variant 1; the human protein sequence corresponds to reference: Q6NSI0 ACCESSION:Q6NSI0 NID: Homo sapiens (Human). Interleukin 17F, isoform 1.

The mouse gene of interest is Il17f (interleukin 17F), ortholog of human IL17F. Aliases include ML1, IL24, ML-1, IL-24, IL-26, IL-17F, cytokine ML-1, and interleukin-24.

IL17F is a cytokine that functions as a signal-transducing ligand, stimulating the production of inflammatory cytokines and chemokines typical of a T-cell helper type 1 (Th1) response. IL17F stimulates production of IL-6, IL-8, granulocyte-macrophage colony stimulating factor (GM-CSF), IL-2, transforming growth factor-beta, and monocyte chemoattractant protein-1 in bronchial epithelial cells or vascular endothelial cells (Kawaguchi et al, *J Biol Chem* 277(18):15229-32 (2002); Starnes et al, *J Immunol* 167(8):4137-40 (2001); Numasake et al, *Immunol Lett* 95(2):175-84 (2004); Kawaguchi et al, *J Allergy Clin Immunol* 114(2):444-50 (2004)). The signaling pathway for IL17F-induced cytokine or chemokine production likely involves activation of extracellular signal-regulated kinase (ERK) 1/2 (Kawaguchi et al, *J Biol Chem* 277(18):15229-32 (2002); Kawaguchi et al, *J Allergy Clin Immunol* 114(2):444-50 (2004)). IL17F plays a role in inhibiting angiogenesis (Starnes et al, *J Immunol* 167(8):4137-40 (2001), inducing neutrophilia, and amplifying antigen-induced allergic responses (Oda et al, *Am J Respir Crit Care Med* 171(1):12-18 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	20	40	18	78
Expected	19.5	39	19.5	78

Chi-Sq.= 9.65 Significance= 0.008026555 (hom/n)= 0.18 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 and 2 were targeted (NCBI accession NM_145856.1).

1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and, in brain, spinal cord, thymus, spleen, and kidney among the 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.69.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA166819-P1381R1C1P1 (UNQ6129))

(a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human interleukin 17F (IL17F) resulted in an increased

anxiety-related response in (-/-) mice. In addition, the mutant (-/-) mice exhibited increased mean serum IgG1, IgG2a and IgG3 levels; increased mean body weight and length as well as increased total tissue mass, lean body mass and total body fat percent and mass with increased bone mineral density measurements. The (-/-) mice exhibited increased mean trabecular bone volume, number and connectivity density. The male (-/-) mice also showed an increasing trend for elevated cholesterol and triglyceride levels. Gene disruption was confirmed by Southern blot.

(b) *Immunology Phenotypic Analysis*

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Serum Immunoglobulin Isotyping Assay:

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains.

5 Any value < 6 is not significant.

Results:

Serum Imm. 2: The (-/-) mice exhibited increased mean serum IgG1, IgG2a and IgG3 levels when compared with those of their (+/+) littermates, the (+/+) mice within the project run, and the historical medians.

10 Mutant (-/-) mice exhibited elevation of IgG1, IgG2a and IgG3 serum immunoglobulins. These immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. The observed phenotype suggests that the PRO20110 polypeptide is a negative regulator of inflammatory responses. These immunological abnormalities suggest that inhibitors (antagonists) of PRO20110 polypeptides would be useful in stimulating the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised
15 patients, such as AIDS sufferers. Accordingly, PRO20110 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(c) *Phenotypic Analysis: CNS/Neurology*

20 In the area of neurology, analysis focused herein on identifying in vivo validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder
25 without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality
30 disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

35 Results:

Stress-Induced Hyperthermia: The male (-/-) mice exhibited increased sensitivity to stress-induced hyperthermia when compared with the level for their gender-matched (+/+) littermates and the historical mean, suggesting an increased anxiety-like response in the mutants.

In summary, the functional observational testing revealed a phenotype associated with increased anxiety which could be associated with mild to moderate anxiety, anxiety due to a general medical condition, and/or bipolar disorders; hyperactivity; sensory disorders; obsessive-compulsive disorders, schizophrenia or a paranoid personality. Thus, PRO20110 polypeptides or agonists thereof would be useful in the treatment of such neurological disorders.

5 (d) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides.

10 *Blood Lipids*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

Results:

Blood Chemistry: Both the male and female (-/-) mice exhibited increased mean serum cholesterol and triglyceride levels when compared with those of their gender-matched (+/+) littermates and the historical means.

20 As summarized above, the (-/-) mice exhibited notably increased mean serum cholesterol and triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO20110 gene can serve as a model for cardiovascular disease. PRO20110 polypeptides or its encoding gene would be useful in regulating blood lipids such as cholesterol and triglycerides. Thus, PRO20110 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, 25 atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, hypertriglyceridemia, diabetes and/or obesity.

(e) *Bone Metabolism & Body Diagnostics*

(1) *Tissue Mass & Lean Body Mass Measurements - DEXA*

DEXA Analysis - Test Description:

30 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in total tissue mass (TTM).

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2,-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, 35 the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI, i.e., whole body, vertebrae, and both femurs).

Body Measurements (Body Length & Weight):

Body Measurements : A measurement of body length and weight was performed at approximately 16

weeks of age.

Results:

Body Weight and Length: The male (-/-) mice exhibited increased mean body weight and mean body length when compared with their gender-matched (+/+) littermates and the historical mean.

(2) Bone Metabolism: Radiology Phenotypic Analysis

5 In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

10 *Dexa Analysis - Test Description:*

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

15 The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImusTM Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

20 *Bone microCT Analysis:*

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

30 DEXA: Both the male and female (-/-) mice exhibited increased mean total tissue mass when compared with that of their gender-matched (+/+) littermates. The male mutants also exhibited increased mean lean body mass, percent total body fat, and total fat mass; the female mutants exhibited increased mean percent total body fat and total fat mass.

35 Micro CT: The male (-/-) mice exhibited increased mean vertebral trabecular bone volume, number and connectivity density when compared with their gender-matched (+/+) littermates and the historical means.

The (-/-) mice analyzed by DEXA and bone micro CT analysis exhibited increased bone measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders such as osteopetrosis. However, the mutant (-/-) mice also exhibited increased body weight and length and total tissue mass and lean body

mass. The female (-/-) mice exhibited an increased mean percentage of body fat and fat mass suggestive of an obesity. These observations suggest that mutant mice deficient in the gene which encodes PRO20110 polypeptides leads to metabolic disorders associated with accumulation of fat but also abnormal bone measurements reflective of osteopetrosis. Thus, PRO20110 polypeptides or agonists thereof would be useful in the treatment of bone related disorders such as osteopetrosis or would be useful in maintaining bone homeostasis. In addition, PRO20110 polypeptides would be useful in maintaining normal lipid metabolism. As well as useful in the treatment of obesity and hypercholesterolemia and hypertriglyceridemia. Antagonists (or inhibitors) of PRO20110 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with abnormal bone metabolism.

66.70. Generation and Analysis of Mice Comprising DNA185171-2994 (UNQ6507) Gene Disruptions

In these knockout experiments, the gene encoding PRO23203 polypeptides (designated as DNA185171-2994) (UNQ6507) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: AK052981 Mus musculus 15 days embryo head cDNA, RIKEN full-length enriched library, clone:D930007L06 product:weakly similar to TUMOR SUPPRESSOR PHYDE [Rattus norvegicus], full insert sequence; protein reference: Q8BWB6 ACCESSION:Q8BWB6 NID: Mus musculus (Mouse). Mus musculus 15 days embryo head cDNA, RIKEN full-length enriched library, clone:D930007L06 product:weakly similar to TUMOR SUPPRESSOR PHYDE; the human gene sequence reference: NM_152999 ACCESSION:NM_152999 NID: gi 25092600 ref NM_152999.2 Homo sapiens six transmembrane epithelial antigen of prostate 2 (STEAP2); the human protein sequence corresponds to reference: Q8NFT2 ACCESSION:Q8NFT2 NID: Homo sapiens (Human). Six-transmembrane epithelial antigen of prostate 2.

The mouse gene of interest is Steap2 (six transmembrane epithelial antigen of prostate 2), ortholog of human STEAP2. Aliases include STMP, IPCA1, IPCA-1, STAMP1, PCANAP1, 4921538B17Rik, prostate cancer associated gene 1, six transmembrane prostate protein, prostate cancer associated protein 1, and SixTransMembrane Protein of Prostate 1.

STEAP2 is an integral membrane protein located primarily in the plasma membrane and trans-Golgi network but also in cytosolic vesicular tubule structures and in endosomes. The protein contains a six transmembrane (6TM) domain that is structurally similar to the 6TM heme-binding domains of NADPH oxidase family members and TedZ bacterial oxidoreductase family members. Expression of STEAP2 is high in prostate gland epithelium but is detectable in other tissues, such as heart, brain, kidney, pancreas, and ovary. STEAP2 may play a role in vesicle transport from the Golgi apparatus to the plasma membrane or in regulated secretion. Because STEAP2 expression is generally higher in prostate cancer cells than in normal prostate epithelial cells, STEAP2 may also play a role in development or progression of prostate cancer (Korkmaz et al, *J Biol Chem* 277(39):36689-96 (2002); Porkka et al, *Lab Invest* 82(11):1573-82 (2002); Sanchez-Pulido et al, *BMC Cancer* 4(1):98 (2004)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}

/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	20	42	20	82
Expected	20.5	41	20.5	82

5 Chi-Sq.= 0.43 Significance= 0.80654144 (hom/n)= 0.27 Avg. Litter Size= 8

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: The exon preceding coding exon 1 and coding exon 1 were targeted (NCBI accession AK052981.1).

10 1. Wild-type Expression Panel: Expression of the target gene was detected in embryonic stem (ES) cells and in all 13 adult tissue samples tested by RT-PCR.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.70.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA185171-2994 (UNQ6507))

(a) OVERALL PHENOTYPIC SUMMARY:

15 Mutation of the gene encoding the ortholog of human six transmembrane epithelial antigen of prostate 2 (STEAP2) resulted in the homozygous mutant mice exhibiting increased mean serum IgG1 and IgG2a responses to ovalbumin challenge when compared with those of their wild-type littermates and the historical means. In addition, the female (-/-) mice exhibited increased anxiety during circadian rhythm testing. Disruption of the target gene was confirmed by Southern hybridization analysis.

20 (b) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

30 Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

35 T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following test was performed:

Ovalbumin Challenge

Procedure: This assay was carried out on 7 wild types and 8 homozygotes. Chicken ovalbumin (OVA) is a T-cell dependent antigen, which is commonly used as a model protein for studying antigen-specific immune responses in mice. OVA is non-toxic and inert and therefore will not cause harm to the animals even if no immune response is induced. The murine immune response to OVA has been well characterized, to the extent that the immunodominant peptides for eliciting T cell responses have been identified. Anti-OVA antibodies are detectable 8 to 10 days after immunization using enzyme-linked immunosorbent assay (ELISA), and determination of different isotypes of antibodies gives further information on the complex processes that may lead to a deficient response in genetically engineered mice.

As noted above, this protocol assesses the ability of mice to raise an antigen-specific immune response. Animals were injected IP with 50 mg of chicken ovalbumin emulsified in Complete Freund's Adjuvant and 14 days later the serum titer of anti-ovalbumin antibodies (IgM, IgG1 and IgG2 subclasses) was measured. The amount of OVA-specific antibody in the serum sample is proportional to the Optical Density (OD) value generated by an instrument that scans a 96-well sample plate. Data was collected for a set of serial dilutions of each serum sample.

Results of this challenge:

Ovalbumin: The (-/-) mice exhibited increased mean serum IgG1 and IgG2a responses to ovalbumin challenge when compared with those of their (+/+) littermates and the historical means.

In summary, the ovalbumin challenge studies indicate that knockout mice deficient in the gene encoding PRO23203 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response when challenged with the T-cell dependent OVA antigen. Thus, antagonists (inhibitors) of PRO23203 polypeptides would be useful for stimulating the immune system and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO23203 polypeptides or agonists thereof, would be useful for inhibiting the

immune response and thus would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

(c) *Phenotypic Analysis: CNS/Neurology*

In the area of neurology, analysis focused herein on identifying in vivo validated targets for the treatment of neurological and psychiatric disorders including depression, generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia and sensory disorders. Neurological disorders include the category defined as "anxiety disorders" which include but are not limited to: mild to moderate anxiety, anxiety disorder due to a general medical condition, anxiety disorder not otherwise specified, generalized anxiety disorder, panic attack, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, substance-induced anxiety disorder, acute alcohol withdrawal, obsessive compulsive disorder, agoraphobia, bipolar disorder I or II, bipolar disorder not otherwise specified, cyclothymic disorder, depressive disorder, major depressive disorder, mood disorder, substance-induced mood disorder. In addition, anxiety disorders may apply to personality disorders including but not limited to the following types: paranoid, antisocial, avoidant behavior, borderline personality disorders, dependent, histrionic, narcissistic, obsessive-compulsive, schizoid, and schizotypal.

Procedure:

Behavioral screens were performed on a cohort of 4 wild type, 4 heterozygous and 8 homozygous mutant mice. All behavioral tests were done between 12 and 16 weeks of age unless reduced viability necessitates earlier testing.

Circadian Test Description:

Female mice are individually housed at 4 pm on the first day of testing in 48.2 cm x 26.5 cm home cages and administered food and water ad libitum. Animals are exposed to a 12-hour light/dark cycle with lights turning on at 7 am and turning off at 7 pm. The system software records the number of beam interruptions caused by the animal's movements, with beam breaks automatically divided into ambulations. Activity is recorded in 60, one-hour intervals during the three-day test. Data generated are displayed by median activity levels recorded for each hour (circadian rhythm) and median total activity during each light/dark cycle (locomotor activity) over the three-day testing period.

Results:

Circadian: The female (-/-) mice exhibited increased median ambulatory counts during the 12-hour habituation and both dark periods when compared with the number for their gender-matched (+/+) littermates and the historical means.

These observations during home-cage activity testing is indicative of hyperactivity and increased anxiety which is consistent with neurological disorders such as generalized anxiety disorders, attention deficit hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders generalized anxiety disorder.

66.71. Generation and Analysis of Mice Comprising DNA171732-3100 (UNQ9574) Gene Disruptions

In these knockout experiments, the gene encoding PRO35250 polypeptides (designated as DNA171732-3100) (UNQ9574) was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: XM_128001 PREDICTED: Mus musculus GPI-anchored HDL-binding

protein 1 (Gpihbp1); protein reference: Q9D1N2 ACCESSION:Q9D1N2 NID: Mus musculus (Mouse). 1110002J19RIK PROTEIN; the human gene sequence reference: NM_178172 Homo sapiens high density lipoprotein-binding protein (LOC338328); the human protein sequence corresponds to reference: Q6P3T2 ACCESSION:Q6P3T2 NID: Homo sapiens (Human). High density lipoprotein-binding protein.

5 The mouse gene of interest is Gpihbp1 (GPI-anchored HDL-binding protein 1), ortholog of human "high density lipoprotein-binding protein." Aliases include GPI-HBP1 and 1110002J19RIK.

Gpihbp1 is a glycosylphosphatidylinositol (GPI)-anchored extracellular membrane protein that functions as a high-density lipoprotein-binding protein. The protein contains a signal peptide, an acidic region, an Ly-6 domain highly conserved among the lymphocyte antigen family, and a hydrophobic C-terminal region. Gpihbp1 is capable of mediating selective lipid uptake but not cholesterol efflux. Gpihbp1 is expressed in liver Kupfer cells, 10 liver sinusoidal epithelium, cardiac muscle cells, bronchial epithelial cells, and alveolar macrophages and is likely to play a role in initial uptake of HDL cholesterol (Ioka et al, *J Biol Chem* 278(9):7344-9 (2003)).

Targeted or gene trap mutations are generated in strain 129SvEv^{Brd}-derived embryonic stem (ES) cells. The chimeric mice are bred to C57BL/6J albino mice to generate F1 heterozygous animals. These progeny are intercrossed to generate F2 wild type, heterozygous, and homozygous mutant progeny. On rare occasions, for 15 example when very few F1 mice are obtained from the chimera, F1 heterozygous mice are crossed to 129SvEv^{Brd}/C57 hybrid mice to yield additional heterozygous animals for the intercross to generate the F2 mice. Level I phenotypic analysis is performed on mice from this generation

	<u>wt</u>	<u>het</u>	<u>hom</u>	<u>Total</u>
Observed	14	58	14	86
20 Expected	21.5	43	21.5	86

Chi-Sq.= 13.97 Significance= 9.2566316E-4 (hom/n)= 0.18 Avg. Litter Size= 9

Mutation Information

Mutation Type: Homologous Recombination (standard)

Description: Coding exons 1 through 4 were targeted (NCBI accession BC061225).

25 1. Wild-type Expression Panel: Expression of the target gene was detected in all 13 adult tissue samples tested by RT-PCR, except brain, eye, skeletal muscle, and bone.

2. QC Expression: Disruption of the target gene was confirmed by Southern hybridization analysis.

66.71.1. PHENOTYPIC ANALYSIS (for disrupted gene: DNA171732-3100 (UNQ9574))

30 (a) OVERALL PHENOTYPIC SUMMARY:

Mutation of the gene encoding the ortholog of human "high density lipoprotein-binding protein" resulted in lipemia in (-/-) mice. Blood chemistry measurements and microscopic analysis revealed that the homozygous mutant mice were notably lipemic. The greatly increased concentration of serum lipids in the mutants affected several other Level 1 parameters, including the total bilirubin measurement and the fundus and angiogram analyses. 35 In addition, the homozygous mutant mice exhibited signs of anemia and immunological abnormalities when compared with the measurements for their wild-type littermates and the historical means. Disruption of the target gene was confirmed by Southern hybridization analysis.

(b) Pathology

Microscopic: Among the 6 (-/-) mice examined, 4 exhibited markedly hyperlipidemic blood at necropsy. Histopathology revealed increased amounts of pale-staining acellular material in scattered blood vessels. In the 4 (-/-) mice with lipemia, the only notable histopathologic alteration was in the cytoplasm of all cells in the zona fasciculata of the adrenal gland which is consistent with the altered lipid/cholesterol uptake or metabolism in these cells. Instead of the normal microvacuolated cytoplasm typical of these cells in normal tissue, the cytoplasm of these cells lacked microvacuoles in the hyperlipidemic mice. Instead, the cytoplasm of the zona fasciculata cells in the mutants was uniformly finely granular and eosinophilic, which would be consistent with altered lipid/cholesterol uptake or metabolism in these cells.

Gene Expression: LacZ activity was not detected in the panel of tissues by immunohistochemical analysis.

(c) Cardiovascular Phenotypic Analysis:

In the area of cardiovascular biology, phenotypic testing was performed to identify potential targets for the treatment of cardiovascular, endothelial or angiogenic disorders. One such phenotypic test included optic fundus photography and angiography to determine the retinal arteriovenous ratio (A/V ratio) in order to flag various eye abnormalities. An abnormal A/V ratio signals such systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to ophthalmological disorders. Such eye abnormalities may include but are not limited to the following: retinal abnormality is retinal dysplasia, various retinopathies, restenosis, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotidemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct ophthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye.

Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMIT+ software. This test takes color photographs through a dilated pupil: the

images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). Many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions.

Results:

Fundus: The (-/-) mice all exhibited semi-transparent retinal vessels that appeared pink in color. The bloodstream could be observed under the fundus microscope, suggesting anomalies of the retinal vasculature in the mutants.

Angiogram: The main retinal vasculature of the (-/-) mice could be clearly visualized with blue light illumination before administration of the fluorescein dye, suggesting increased fluorescent material was already present in the blood of the mutant mice. After administration of the fluorescein dye, no notable difference was observed between the (-/-) mice and their (+/+) littermates.

(d) Immunology Phenotypic Analysis

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, etc. The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, i.e., lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases (such as rheumatoid arthritis, immune mediated renal disease, hepatobiliary diseases, inflammatory bowel disease (IBD), psoriasis, and asthma), non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, and graft rejection, etc. In the

area of immunology, targets were identified for the treatment of inflammation and inflammatory disorders.

In the area of immunology, targets have been identified herein for the treatment of inflammation and inflammatory disorders. Immune related diseases, in one instance, could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

The following tests were performed:

(1) *Hematology*

Test Description: Blood tests are carried out by Abbott's Cell-Dyn 3500R, an automated hematology analyzer. Some of its features include a five-part WBC differential. 'Patient' reports can cover over 22 parameters in all.

Results:

Hematology: The (-/-) mice exhibited a notably increased mean absolute neutrophil count and a decreased mean absolute lymphocyte count when compared with those of their (+/+) littermates and the historical means. The (-/-) mice also exhibited a decreased mean red blood cell count and a decreased mean hematocrit level. In addition, the (-/-) mice exhibited increased mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell distribution width, suggesting that the red blood cells in the mutant mice are a little larger than normal with increased variation in size.

These results are related to a phenotype associated with anemia. Thus, PRO35250 polypeptides, agonists thereof or the encoding gene for PRO35350 polypeptides must be essential for normal red blood cell production and as such would be useful in the treatment of blood disorders associated with anemia or a low hematocrit.

(2) *Acute Phase Response:*

Test Description: Bacterial lipopolysaccharide (LPS) is an endotoxin, and as such is a potent inducer of an acute phase response and systemic inflammation. The Level I LPS mice were injected intraperitoneally (i.p.) with a sublethal dose of LPS in 200 μ L sterile saline using a 26 gauge needle. The doses were based on the average weight of the mice tested at 1 μ g/g body weight 3 hours after injection; a 100ul blood sample was then taken and analyzed for the presence of TNFa, MCP-1, and IL-6 on the FACS Calibur instrument.

Results:

Acute Phase Response: The (-/-) mice exhibited a notably increased mean serum IL-6 response to LPS challenge when compared with that of their (+/+) littermates and the historical mean.

In summary, the LPS endotoxin challenge demonstrated that knockout mice deficient in the gene encoding PRO35250 polypeptides exhibit immunological abnormalities when compared with their wild-type littermates. In particular, the mutant mice exhibited an increased ability to elicit an immunological response (IL-6 production) when challenged with the LPS endotoxin indicating a pro-inflammatory response. IL-6 contributes to the later stages of B cell activation. In addition, IL-6 plays a critical role in inducing the acute phase response and systemic inflammation. Thus, PRO35250 polypeptides function as a negative regulator of the immune response.

(3) *Serum Immunoglobulin Isotyping Assay:*

The Serum Immunoglobulin Isotyping Assay is performed using a Cytometric Bead Array (CBA) kit. This

assay is used to rapidly identify the heavy and light chain isotypes of a mouse monoclonal antibody in a single sample. The values expressed are "relative fluorescence units" and are based on the detection of kappa light chains. Any value < 6 is not significant.

Results:

5 Serum Imm. 2: The (-/-) mice exhibited an increased mean serum IgM level and an increased mean serum IgG3 level when compared with that of their (+/+) littermates, the (+/+) mice within the project run, and the historical medians.

10 Mutant (-/-) mice exhibited elevation of IgM serum immunoglobulins compared to their gender-matched (+/+) littermates. IgM immunoglobulins are the first to be produced in a humoral immune response for neutralization of bacterial toxins and are particularly important in activating the complement system. The mutant (-/-) mice also exhibited elevation of IgG3 serum immunoglobulins compared to their gender-matched (+/+) littermates. These immunoglobulins have neutralization effects and to a lesser extent are important for activation of the complement system. The observed phenotype suggests that the PRO35250 polypeptide is a negative regulator of inflammatory responses. These immunological abnormalities suggest that inhibitors (antagonists) of PRO35250 polypeptides would be important agents which could stimulate the immune system (such as T cell proliferation) and would find utility in the cases wherein this effect would be beneficial to the individual such as in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers. Accordingly, PRO35250 polypeptides or agonists thereof would be useful in inhibiting the immune response and would be useful candidates for suppressing harmful immune responses, e.g. in the case of graft rejection or graft-versus-host diseases.

20 (e) *Phenotypic Analysis: Cardiology*

In the area of cardiovascular biology, targets were identified herein for the treatment of hypertension, atherosclerosis, heart failure, stroke, various coronary artery diseases, dyslipidemias such as high cholesterol (hypercholesterolemia) and elevated serum triglycerides (hypertriglyceridemia), diabetes and/or obesity. The phenotypic tests included the measurement of serum cholesterol and triglycerides. In addition to measuring blood lipid levels the following blood chemistry tests are also routinely performed: Alkaline Phosphatase; Alanine Amino-Transferase; Albumin; Bilirubin; Phosphorous; Creatinine; BUN = Blood Urea Nitrogen; Calcium; Uric Acid; Sodium; Potassium; and Chloride.

Blood Lipids & Blood Chemistry Results

30 Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. High cholesterol levels and increased triglyceride blood levels are recognized risk factors in the development of cardiovascular disease and/or diabetes. Measuring blood lipids facilitates the finding of biological switches that regulate blood lipid levels. Inhibition of factors which elevate blood lipid levels may be useful for reducing the risk for cardiovascular disease. In these blood chemistry tests, measurements were recorded using the COBAS Integra 400 (mfr: Roche).

35 Results:

Blood Chemistry: Both the male and female (-/-) mice exhibited enormously elevated mean serum cholesterol (>11 SD above the mean) and triglyceride (~214 SD above the mean) levels. Alkaline phosphatase levels were also elevated as well as total bilirubin (~29 times the normal) and decreased calcium levels (8 SD below the mean)

when compared with those of their gender-matched (+/+) littermates and the historical means.

As summarized above, the (-/-) mice exhibited notably increased mean serum cholesterol and triglyceride levels when compared with their gender-matched (+/+) littermates and the historical means. Thus, mutant mice deficient in the PRO35250 gene can serve as a model for cardiovascular disease. PRO35250 polypeptides or its encoding gene would be useful in regulating blood lipids such as cholesterol and triglycerides. Thus, PRO35250 polypeptides or agonists thereof would be useful in the treatment of such cardiovascular diseases as hypertension, atherosclerosis, heart failure, stroke, various coronary diseases, hypercholesterolemia, hypertriglyceridemia, diabetes and/or obesity.

The (-/-) mice exhibited notably decreased mean serum calcium, sodium, and chloride levels. The (-/-) mice also exhibited an increased mean serum bilirubin level; however, the notable lipemia in the mutant samples could have skewed this reading, since the presence of even slight lipemia is known to affect the reliability of bilirubin measurements. The depressed levels of sodium and chloride are an indication of an electrolyte imbalance. The decreased mean serum calcium levels could be indicative of the increased alkaline phosphatase activity noted above.

(f) *Bone Metabolism: Radiology Phenotypic Analysis*

In the area of bone metabolism, targets were identified herein for the treatment of arthritis, osteoporosis, osteopenia and osteopetrosis as well as identifying targets that promote bone healing. Tests included:

- DEXA for measurement of bone mineral density on femur and vertebra
- MicroCT for very high resolution and very high sensitivity measurements of bone mineral density for both trabecular and cortical bone.

Dexa Analysis - Test Description:

Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Dual Energy X-ray Absorptiometry (DEXA) has been used successfully to identify changes in bone. Anesthetized animals were examined and bone mineral content (BMC), BMC/LBM ratios, volumetric bone mineral density (vBMD), total body BMD, femur BMD and vertebra BMD were measured.

The mouse was anesthetized by intraperitoneal injection of Avertin (1.25% 2,2,2-tribromoethanol, 20 ml/kg body weight), body length and weight were measured, and then the mouse was placed in a prone position on the platform of the PIXImus™ Densitometer (Lunar Inc.) for a DEXA scan. Using Lunar PIXImus software, the bone mineral density (BMD) and fat composition (% fat) and total tissue mass (TTM) were determined in the regions of interest (ROI) [i.e., whole body, vertebrae, and both femurs].

Bone microCT Analysis:

Procedure: MicroCT was also used to get very sensitive measurements of BMD. One vertebra and 1 femur were taken from a cohort of 4 wild type and 8 homozygous mice. Measurements were taken of lumbar 5 vertebra trabecular bone volume, trabecular thickness, connectivity density and midshaft femur total bone area and cortical thickness. The μ CT40 scans provided detailed information on bone mass and architecture. Multiple bones were placed into sample holders and scanned automatically. Instrument software was used to select regions of interest for analysis. Trabecular bone parameters were analyzed in the fifth lumbar vertebrae (LV5) at 16 micrometer resolution and cortical bone parameters were analyzed in the femur midshaft at a resolution of 20 micrometers.

Results:

Micro CT: The male (-/-) mice exhibited increased mean vertebral trabecular number and connectivity density when compared with that of their gender-matched (+/+) littermates and the historical means.

The (-/-) mice analyzed by bone micro CT analysis exhibited increased bone measurements when compared with their (+/+) littermates, suggestive of abnormal bone disorders such as osteopetrosis. These observations suggest that mutant mice deficient in the gene which encodes PRO35250 polypeptides leads to metabolic disorders abnormal bone measurements reflective of osteopetrosis. Thus, PRO35250 polypeptides or agonists thereof would be useful in the treatment of bone related disorders such as osteopetrosis or would be useful in maintaining bone homeostasis. Antagonists (or inhibitors) of PRO35250 polypeptides or its encoding gene would lead to abnormal or pathological bone disorders including inflammatory diseases associated with abnormal bone metabolism.

EXAMPLE 67: Use of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 as a hybridization probe

The following method describes use of a nucleotide sequence encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540,

PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO69122-, PRO204-, PRO214-, PRO222-, PRO234-, PRO265-, PRO309-, PRO332-, PRO342-, PRO356-, PRO540-, PRO618-, PRO944-, PRO994-, PRO1079-, PRO1110-, PRO1122-, PRO1138-, PRO1190-, PRO1272-, PRO1286-, PRO1295-, PRO1309-, PRO1316-, PRO1383-, PRO1384-, PRO1431-, PRO1434-, PRO1475-, PRO1481-, PRO1568-, PRO1573-, PRO1599-, PRO1604-, PRO1605-, PRO1693-, PRO1753-, PRO1755-, PRO1777-, PRO1788-, PRO1864-, PRO1925-, PRO1926-, PRO3566-, PRO4330-, PRO4423-, PRO36935-, PRO4977-, PRO4979-, PRO4980-, PRO4981-, PRO5801-, PRO5995-, PRO6001-, PRO6095-, PRO6182-, PRO7170-, PRO7171-, PRO7436-, PRO9912-, PRO9917-, PRO37337-, PRO37496-, PRO19646-, PRO21718-, PRO19820-, PRO21201-, PRO20026-, PRO20110-, PRO23203- or PRO35250-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides can then be identified using standard techniques known in the art.

EXAMPLE 68: Expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 in *E. coli*.

This example illustrates preparation of an unglycosylated form of PRO69122, PRO204, PRO214,

PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides by recombinant expression in *E. coli*.

The DNA sequence encoding a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell

pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final

concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer.

5 The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

10 The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein
15 is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.
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Fractions containing the desired folded PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431,
25 PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.
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35 EXAMPLE 69: Expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,

PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 in mammalian cells

This example illustrates preparation of a potentially glycosylated form of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-PRO69122, pRK5-PRO204, pRK5-PRO214, pRK5-PRO222, pRK5-PRO234, pRK5-PRO265, pRK5-PRO309, pRK5-PRO332, pRK5-PRO342, pRK5-PRO356, pRK5-PRO540, pRK5-PRO618, pRK5-PRO944, pRK5-PRO994, pRK5-PRO1079, pRK5-PRO1110, pRK5-PRO1122, pRK5-PRO1138, pRK5-PRO1190, pRK5-PRO1272, pRK5-PRO1286, pRK5-PRO1295, pRK5-PRO1309, pRK5-PRO1316, pRK5-PRO1383, pRK5-PRO1384, pRK5-PRO1431, pRK5-PRO1434, pRK5-PRO1475, pRK5-PRO1481, pRK5-PRO1568, pRK5-PRO1573, pRK5-PRO1599, pRK5-PRO1604, pRK5-PRO1605, pRK5-PRO1693, pRK5-PRO1753, pRK5-PRO1755, pRK5-PRO1777, pRK5-PRO1788, pRK5-PRO1864, pRK5-PRO1925, pRK5-PRO1926, pRK5-PRO3566, pRK5-PRO4330, pRK5-PRO4423, pRK5-PRO36935, pRK5-PRO4977, pRK5-PRO4979, pRK5-PRO4980, pRK5-PRO4981, pRK5-PRO5801, pRK5-PRO5995, pRK5-PRO6001, pRK5-PRO6095, pRK5-PRO6182, pRK5-PRO7170, pRK5-PRO7171, pRK5-PRO7436, pRK5-PRO9912, pRK5-

PRO9917, pRK5-PRO37337, pRK5-PRO37496, pRK5-PRO19646, pRK5-PRO21718, pRK5-PRO19820, pRK5-PRO21201, pRK5-PRO20026, pRK5-PRO20110, pRK5-PRO23203 or pRK5-PRO35250.

The selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO69122, pRK5-PRO204, pRK5-PRO214, pRK5-PRO222, pRK5-PRO234, pRK5-PRO265, pRK5-PRO309, pRK5-PRO332, pRK5-PRO342, pRK5-PRO356, pRK5-PRO540, pRK5-PRO618, pRK5-PRO944, pRK5-PRO994, pRK5-PRO1079, pRK5-PRO1110, pRK5-PRO1122, pRK5-PRO1138, pRK5-PRO1190, pRK5-PRO1272, pRK5-PRO1286, pRK5-PRO1295, pRK5-PRO1309, pRK5-PRO1316, pRK5-PRO1383, pRK5-PRO1384, pRK5-PRO1431, pRK5-PRO1434, pRK5-PRO1475, pRK5-PRO1481, pRK5-PRO1568, pRK5-PRO1573, pRK5-PRO1599, pRK5-PRO1604, pRK5-PRO1605, pRK5-PRO1693, pRK5-PRO1753, pRK5-PRO1755, pRK5-PRO1777, pRK5-PRO1788, pRK5-PRO1864, pRK5-PRO1925, pRK5-PRO1926, pRK5-PRO3566, pRK5-PRO4330, pRK5-PRO4423, pRK5-PRO36935, pRK5-PRO4977, pRK5-PRO4979, pRK5-PRO4980, pRK5-PRO4981, pRK5-PRO5801, pRK5-PRO5995, pRK5-PRO6001, pRK5-PRO6095, pRK5-PRO6182, pRK5-PRO7170, pRK5-PRO7171, pRK5-PRO7436, pRK5-PRO9912, pRK5-PRO9917, pRK5-PRO37337, pRK5-PRO37496, pRK5-PRO19646, pRK5-PRO21718, pRK5-PRO19820, pRK5-PRO21201, pRK5-PRO20026, pRK5-PRO20110, pRK5-PRO23203 or pRK5-PRO35250 DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml ³⁵S-cysteine and 200 µCi/ml ³⁵S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755,

PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 may be introduced into 293 cells transiently using the dextran sulfate method described by Sompayrac et al., *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to

5 maximal density in a spinner flask and 700 µg pRK5-PRO69122, pRK5-PRO204, pRK5-PRO214, pRK5-PRO222, pRK5-PRO234, pRK5-PRO265, pRK5-PRO309, pRK5-PRO332, pRK5-PRO342, pRK5-PRO356, pRK5-PRO540, pRK5-PRO618, pRK5-PRO944, pRK5-PRO994, pRK5-PRO1079, pRK5-PRO1110, pRK5-PRO1122, pRK5-PRO1138, pRK5-PRO1190, pRK5-PRO1272, pRK5-PRO1286, pRK5-PRO1295, pRK5-PRO1309, pRK5-PRO1316, pRK5-PRO1383, pRK5-PRO1384, pRK5-PRO1431, pRK5-PRO1434, pRK5-PRO1475, pRK5-PRO1481, pRK5-PRO1568, pRK5-PRO1573, pRK5-PRO1599, pRK5-PRO1604, pRK5-PRO1605, pRK5-PRO1693, pRK5-PRO1753, pRK5-PRO1755, pRK5-PRO1777, pRK5-PRO1788, pRK5-PRO1864, pRK5-PRO1925, pRK5-PRO1926, pRK5-PRO3566, pRK5-PRO4330, pRK5-PRO4423, pRK5-PRO36935, pRK5-PRO4977, pRK5-PRO4979, pRK5-PRO4980, pRK5-PRO4981, pRK5-PRO5801, pRK5-PRO5995, pRK5-PRO6001, pRK5-PRO6095, pRK5-PRO6182, pRK5-PRO7170, pRK5-PRO7171, pRK5-PRO7436, pRK5-PRO9912, pRK5-PRO9917, pRK5-PRO37337, pRK5-PRO37496, pRK5-PRO19646, pRK5-PRO21718, pRK5-PRO19820, pRK5-PRO21201, pRK5-PRO20026, pRK5-PRO20110, pRK5-PRO23203 or pRK5-PRO35250 DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture

10 medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

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PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can be expressed in CHO cells. The pRK5-PRO69122, pRK5-PRO204, pRK5-PRO214, pRK5-PRO222, pRK5-PRO234, pRK5-PRO265, pRK5-PRO309, pRK5-PRO332, pRK5-PRO342, pRK5-

PRO356, pRK5-PRO540, pRK5-PRO618, pRK5-PRO944, pRK5-PRO994, pRK5-PRO1079, pRK5-PRO1110, pRK5-PRO1122, pRK5-PRO1138, pRK5-PRO1190, pRK5-PRO1272, pRK5-PRO1286, pRK5-PRO1295, pRK5-PRO1309, pRK5-PRO1316, pRK5-PRO1383, pRK5-PRO1384, pRK5-PRO1431, pRK5-PRO1434, pRK5-PRO1475, pRK5-PRO1481, pRK5-PRO1568, pRK5-PRO1573, pRK5-PRO1599, pRK5-PRO1604, pRK5-PRO1605, pRK5-PRO1693, pRK5-PRO1753, pRK5-PRO1755, pRK5-PRO1777, pRK5-PRO1788, pRK5-PRO1864, pRK5-PRO1925, pRK5-PRO1926, pRK5-PRO3566, pRK5-PRO4330, pRK5-PRO4423, pRK5-PRO36935, pRK5-PRO4977, pRK5-PRO4979, pRK5-PRO4980, pRK5-PRO4981, pRK5-PRO5801, pRK5-PRO5995, pRK5-PRO6001, pRK5-PRO6095, pRK5-PRO6182, pRK5-PRO7170, pRK5-PRO7171, pRK5-PRO7436, pRK5-PRO9912, pRK5-PRO9917, pRK5-PRO37337, pRK5-PRO37496, pRK5-PRO19646, pRK5-PRO21718, pRK5-PRO19820, pRK5-PRO21201, pRK5-PRO20026, pRK5-PRO20110, pRK5-PRO23203 or pRK5-PRO35250 can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can then be concentrated and purified by any selected method.

Epitope-tagged PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 may also be expressed in host CHO cells. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944,

PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and

CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779) (1996), and uses the SV40 early promoter/enhancer
5 to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Dosper® or Fugene® (Boehringer
10 Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2
15 μ m filtered PS20 with 5% 0.2 μ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^5 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production
20 medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary
25 to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is
30 pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 mL/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 mL G25 Superfine (Pharmacia) column and stored at -80°C.

35 Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions

into tubes containing 275 μ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

5 EXAMPLE 70: Expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332,
PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190,
PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475,
PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,
PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,
PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436,
10 PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026,
PRO20110, PRO23203 or PRO35250 in Yeast

The following method describes recombinant expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 in yeast.

20 First, yeast expression vectors are constructed for intracellular production or secretion of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 from the ADH2/GAPDH promoter. DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383,

PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250. For secretion, DNA encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,

PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 may further be purified using selected column chromatography resins.

EXAMPLE 71: Expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 in Baculovirus-infected insect cells.

The sequence coding for PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A

variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 or the desired portion of the coding sequence of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with

25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A_{280} with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A_{280} baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni^{2+} -NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

EXAMPLE 72: Preparation of Antibodies that Bind PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801,

PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides, fusion proteins containing PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides, and cells expressing recombinant PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be

boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001,

PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 73: Purification of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 Polypeptides Using Specific Antibodies

Native or recombinant PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO69122, pro-PRO204, pro-PRO214, pro-PRO222, pro-PRO234, pro-PRO265, pro-PRO309, pro-PRO332, pro-PRO342, pro-PRO356, pro-PRO540, pro-PRO618, pro-PRO944, pro-PRO994, pro-PRO1079, pro-PRO1110, pro-PRO1122, pro-PRO1138, pro-PRO1190, pro-PRO1272, pro-PRO1286, pro-PRO1295, pro-PRO1309, pro-PRO1316, pro-PRO1383, pro-PRO1384, pro-PRO1431, pro-

PRO1434, pro-PRO1475, pro-PRO1481, pro-PRO1568, pro-PRO1573, pro-PRO1599, pro-PRO1604, pro-
 PRO1605, pro-PRO1693, pro-PRO1753, pro-PRO1755, pro-PRO1777, pro-PRO1788, pro-PRO1864, pro-
 PRO1925, pro-PRO1926, pro-PRO3566, pro-PRO4330, pro-PRO4423, pro-PRO36935, pro-PRO4977, pro-
 PRO4979, pro-PRO4980, pro-PRO4981, pro-PRO5801, pro-PRO5995, pro-PRO6001, pro-PRO6095, pro-
 PRO6182, pro-PRO7170, pro-PRO7171, pro-PRO7436, pro-PRO9912, pro-PRO9917, pro-PRO37337, pro-
 5 PRO37496, pro-PRO19646, pro-PRO21718, pro-PRO19820, pro-PRO21201, pro-PRO20026, pro-PRO20110,
 pro-PRO23203 or pro-PRO35250 polypeptide, mature PRO69122, mature PRO204, mature PRO214, mature
 PRO222, mature PRO234, mature PRO265, mature PRO309, mature PRO332, mature PRO342, mature PRO356,
 mature PRO540, mature PRO618, mature PRO944, mature PRO994, mature PRO1079, mature PRO1110, mature
 PRO1122, mature PRO1138, mature PRO1190, mature PRO1272, mature PRO1286, mature PRO1295, mature
 10 PRO1309, mature PRO1316, mature PRO1383, mature PRO1384, mature PRO1431, mature PRO1434, mature
 PRO1475, mature PRO1481, mature PRO1568, mature PRO1573, mature PRO1599, mature PRO1604, mature
 PRO1605, mature PRO1693, mature PRO1753, mature PRO1755, mature PRO1777, mature PRO1788, mature
 PRO1864, mature PRO1925, mature PRO1926, mature PRO3566, mature PRO4330, mature PRO4423, mature
 PRO36935, mature PRO4977, mature PRO4979, mature PRO4980, mature PRO4981, mature PRO5801, mature
 15 PRO5995, mature PRO6001, mature PRO6095, mature PRO6182, mature PRO7170, mature PRO7171, mature
 PRO7436, mature PRO9912, mature PRO9917, mature PRO37337, mature PRO37496, mature PRO19646, mature
 PRO21718, mature PRO19820, mature PRO21201, mature PRO20026, mature PRO20110, mature PRO23203
 or mature PRO35250 polypeptide, or pre-PRO69122, pre-PRO204, pre-PRO214, pre-PRO222, pre-PRO234, pre-
 PRO265, pre-PRO309, pre-PRO332, pre-PRO342, pre-PRO356, pre-PRO540, pre-PRO618, pre-PRO944, pre-
 20 PRO994, pre-PRO1079, pre-PRO1110, pre-PRO1122, pre-PRO1138, pre-PRO1190, pre-PRO1272, pre-
 PRO1286, pre-PRO1295, pre-PRO1309, pre-PRO1316, pre-PRO1383, pre-PRO1384, pre-PRO1431, pre-
 PRO1434, pre-PRO1475, pre-PRO1481, pre-PRO1568, pre-PRO1573, pre-PRO1599, pre-PRO1604, pre-
 PRO1605, pre-PRO1693, pre-PRO1753, pre-PRO1755, pre-PRO1777, pre-PRO1788, pre-PRO1864, pre-
 PRO1925, pre-PRO1926, pre-PRO3566, pre-PRO4330, pre-PRO4423, pre-PRO36935, pre-PRO4977, pre-
 25 PRO4979, pre-PRO4980, pre-PRO4981, pre-PRO5801, pre-PRO5995, pre-PRO6001, pre-PRO6095, pre-
 PRO6182, pre-PRO7170, pre-PRO7171, pre-PRO7436, pre-PRO9912, pre-PRO9917, pre-PRO37337, pre-
 PRO37496, pre-PRO19646, pre-PRO21718, pre-PRO19820, pre-PRO21201, pre-PRO20026, pre-PRO20110,
 pre-PRO23203 or pre-PRO35250 polypeptide is purified by immunoaffinity chromatography using antibodies
 specific for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342,
 30 PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190,
 PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475,
 PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,
 PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,
 PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436,
 35 PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026,
 PRO20110, PRO23203 or PRO35250 polypeptide of interest. In general, an immunoaffinity column is constructed
 by covalently coupling the anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-
 PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944,

anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by preparing a fraction from cells containing PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,

PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO69122, antibody/PRO204, antibody/PRO214, antibody/PRO222, antibody/PRO234, antibody/PRO265, antibody/PRO309, antibody/PRO332, antibody/PRO342, antibody/PRO356, antibody/PRO540, antibody/PRO618, antibody/PRO944, antibody/PRO994, antibody/PRO1079, antibody/PRO1110, antibody/PRO1122, antibody/PRO1138, antibody/PRO1190, antibody/PRO1272, antibody/PRO1286, antibody/PRO1295, antibody/PRO1309, antibody/PRO1316, antibody/PRO1383, antibody/PRO1384, antibody/PRO1431, antibody/PRO1434, antibody/PRO1475, antibody/PRO1481, antibody/PRO1568, antibody/PRO1573, antibody/PRO1599, antibody/PRO1604, antibody/PRO1605, antibody/PRO1693, antibody/PRO1753, antibody/PRO1755, antibody/PRO1777, antibody/PRO1788, antibody/PRO1864, antibody/PRO1925, antibody/PRO1926, antibody/PRO3566, antibody/PRO4330, antibody/PRO4423, antibody/PRO36935, antibody/PRO4977, antibody/PRO4979, antibody/PRO4980, antibody/PRO4981, antibody/PRO5801, antibody/PRO5995, antibody/PRO6001, antibody/PRO6095, antibody/PRO6182, antibody/PRO7170, antibody/PRO7171, antibody/PRO7436, antibody/PRO9912, antibody/PRO9917, antibody/PRO37337, antibody/PRO37496, antibody/PRO19646, antibody/PRO21718, antibody/PRO19820, antibody/PRO21201, antibody/PRO20026, antibody/PRO20110, antibody/PRO23203 or antibody/PRO35250 polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is collected.

EXAMPLE 74: Drug Screening

This invention is particularly useful for screening compounds by using PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138,

PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragment, or (ii) for the presence of a complex between the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250

polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragment is typically labeled. After suitable incubation, free PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or to interfere with the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431,

PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the peptide test compounds are

5 reacted with PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980,

10 PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide and washed. Bound PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384,

15 PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide is detected by methods

20 well known in the art. Purified PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,

25 PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

30 This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777,

35 PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide specifically compete with a test compound for binding to

PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

EXAMPLE 75: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide or which enhance or interfere with the function of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599,

PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide *in vivo* (c.f., Hodgson, Bio/Technology, 9: 19-21 (1991)).

5 In one approach, the three-dimensional structure of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, or of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO69122,

PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

WHAT IS CLAIMED IS:

1. A method of identifying a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:
- 5 (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;
- 10 (b) measuring a physiological characteristic of the non-human transgenic animal; and
- 15 (c) comparing the measured physiological characteristic with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal.
- 20 2. The method of Claim 1, wherein the non-human transgenic animal is heterozygous for the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.
- 25 3. The method of Claim 1, wherein the phenotype exhibited by the non-human transgenic animal as compared with gender matched wild-type littermates is at least one of the following: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological
- 30 35

disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

4. The method of Claim 3, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

5 5. The method of Claim 3, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

6. The method of Claim 3, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

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7. The method of Claim 3, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

8. The method of Claim 3, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

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9. The method of Claim 3, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

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10. The method of Claim 3, wherein the eye abnormality is a retinal abnormality.

11. The method of Claim 3, wherein the eye abnormality is consistent with vision problems or blindness.

25 12. The method of Claim 10, wherein the retinal abnormality is consistent with retinitis pigmentosa.

13. The method of Claim 10, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

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14. The method of Claim 10, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger

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syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotidemia, cystinosis, Wolfram syndrome,
 5 Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

15. The method of Claim 3, wherein the eye abnormality is a cataract.

10 16. The method of Claim 15, wherein the cataract is consistent with systemic diseases such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

15 17. The method of Claim 3, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

18. The method of Claim 3, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure;
 20 hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e.g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other
 25 injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

19. The method of Claim 3, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic
 30 inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the
 35 central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel

disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

20. The method of Claim 3, wherein the bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

21. The method of Claim 1, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased

mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization

of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

22. An isolated cell derived from a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

23. The isolated cell of Claim 22 which is a murine cell.

24. The isolated cell of Claim 23, wherein the murine cell is an embryonic stem cell.

25. The isolated cell of Claim 22, wherein the non-human transgenic animal exhibits at least one of the following phenotypes compared with gender matched wild-type littermates: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

26. A method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,

PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

27. The method of Claim 26, wherein the phenotype associated with the gene disruption comprises a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

28. The method of Claim 27, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

29. The method of Claim 27, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

30. The method of Claim 27, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

31. The method of Claim 27, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

32. The method of Claim 27, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.
33. The method of Claim 27, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.
34. The method of Claim 27, wherein the eye abnormality is a retinal abnormality.
35. The method of Claim 27, wherein the eye abnormality is consistent with vision problems or blindness.
36. The method of Claim 34, wherein the retinal abnormality is consistent with retinitis pigmentosa.
37. The method of Claim 34, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.
38. The method of Claim 34, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphyseal congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemelia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.
39. The method of Claim 27, wherein the eye abnormality is a cataract.
40. The method of Claim 39, wherein the cataract is consistent with systemic diseases such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

41. The method of Claim 27, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

42. The method of Claim 27, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

43. The method of Claim 27, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis; Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation-associated diseases including graft rejection and graft-versus-host disease.

44. The method of Claim 27, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

45. The method of Claim 26, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open

field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T

cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

46. An agent identified by the method of Claim 26.

47. The agent of Claim 46 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

48. The agent of Claim 47, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

49. The agent of Claim 47, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

50. A method of identifying an agent that modulates a physiological characteristic associated with a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434,

PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

- 5 (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788,
- 10 PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;
- (b) measuring a physiological characteristic exhibited by the non-human transgenic animal of (a);
- 15 (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic exhibited by the non-human transgenic animal that differs from the physiological characteristic exhibited by the wild-type animal is identified as a physiological characteristic associated with gene disruption;
- (d) administering a test agent to the non-human transgenic animal of (a); and
- 20 (e) determining whether the physiological characteristic associated with gene disruption is modulated.

51. The method of Claim 50, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm;
- 25 increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during
- 30 prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermidalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve
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abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels; increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow; increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD);

increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

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52. An agent identified by the method of Claim 50.

53. The agent of Claim 52 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

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54. The agent of Claim 53, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250antibody.

55. The agent of Claim 53, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250antibody.

56. A method of identifying an agent which modulates a behavior associated with a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979,

PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) observing the behavior exhibited by the non-human transgenic animal of (a);

5 (c) comparing the observed behavior of (b) with that of a gender matched wild-type animal, wherein the observed behavior exhibited by the non-human transgenic animal that differs from the observed behavior exhibited by the wild-type animal is identified as a behavior associated with gene disruption;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the agent modulates the behavior associated with gene disruption.

10 57. The method of Claim 56, wherein the behavior is an increased anxiety-like response during open field activity testing.

58. The method of Claim 56, wherein the behavior is a decreased anxiety-like response during open field activity testing.

15 59. The method of Claim 56, wherein the behavior is an abnormal circadian rhythm during home-cage activity testing.

20 60. The method of Claim 56, wherein the behavior is an enhanced motor coordination during inverted screen testing.

61. The method of Claim 56, wherein the behavior is an impaired motor coordination during inverted screen testing.

25 62. The method of Claim 56, wherein the behavior is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

30 63. An agent identified by the method of Claim 56.

64. The agent of Claim 63 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, 35 PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

65. The agent of Claim 64, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250antibody.

66. The agent of Claim 64, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250antibody.

67. A method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481,

PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

- 5 (b) administering a test agent to said non-human transgenic animal; and
- (c) determining whether said test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in the non-human transgenic animal.

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68. The method of Claim 67, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

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69. The method of Claim 67, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

70. The method of Claim 67, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

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71. The method of Claim 67, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

72. The method of Claim 67, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

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73. The method of Claim 73, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

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74. The method of Claim 67, wherein the eye abnormality is a retinal abnormality.

75. The method of Claim 67, wherein the eye abnormality is consistent with vision problems or blindness.

76. The method of Claim 74, wherein the retinal abnormality is consistent with retinitis pigmentosa.

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77. The method of Claim 74, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

78. The method of Claim 74, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedrich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

79. The method of Claim 67, wherein the eye abnormality is a cataract.

80. The method of Claim 79, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

81. The method of Claim 67, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

82. The method of Claim 67, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e.g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

83. The method of Claim 67, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic

inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

84. The method of Claim 67, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

85. The method of Claim 67, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: increased anxiety-like response during open field testing; decreased anxiety during open field testing; hypoactivity with no circadian rhythm; increased total distance traveled during open field testing (hyperactivity); decreased locomotor activity during open field testing; abnormal circadian rhythm during home-cage activity testing (low activity during the light phase); abnormal circadian rhythm during home-cage activity testing including decreased ambulatory counts; abnormal circadian rhythm during home-cage activity testing including increased ambulatory counts; whiskers absent due to anxiety phenotype; enhanced circadian rhythm; increased stress induced hyperthermia with increased stress response (increased anxiety); increased resistance to stress induced hyperthermia; decreased resistance to stress induced hyperthermia; enhanced motor coordination during inverted screen testing; impaired motor coordination during inverted screen testing; increased immobility in tail suspension (increased depressive-like response); increased depressive-like response during tail suspension testing; decreased depressive-like response during tail suspension testing; clutched hind limbs during tail suspension testing; decreased startle response during prepulse inhibition testing; no startle response indicating deafness; increased prepulse inhibition with enhanced sensorimotor gating/attention; increased latency on hotplate indicative of decreased sensitivity to heat-induced pain; ophthalmological abnormalities; corneal epidermalization of the corneal stroma with scarring and blocked vision; metaplasia of the cornea and sclera; attenuated retinal arteries; retinal hemorrhage; optic nerve abnormalities; dilated optic disc; increased intraocular pressure; corneal epithelialization with underdeveloped eyelids; retinal degeneration; agenesis of the Harderian gland; retinal vessel disorganization, microaneurysms and retinal capillary leakage; impaired vision; decreased heart rate; decreased mean systolic blood pressure; increased

mean systolic blood pressure; increased insulin sensitivity; increased mean fasting serum glucose levels; decreased mean serum glucose levels; increased mean serum cholesterol levels; decreased mean serum cholesterol levels; increased mean serum triglyceride levels; enhanced glucose tolerance; impaired glucose tolerance; decreased mean serum insulin levels; ketonemia; decreased mean serum calcium; blood urobilinogen, nitrites, protein and ketones; decreased sodium and chloride; increased bilirubin; notable lipemia; increased uric acid and potassium levels;

5 increased mean serum alkaline phosphatase levels; decreased mean serum alkaline phosphatase levels; blood in the urine; glucosuria; increased nitrituria; ketonuria; increased mean percentage of natural killer cells; decreased mean percentage of natural killer cells; abnormal leukocyte count; leukopenia due to lymphopenia and granulocytopenia; increased mean percentage of CD4 cells; decreased mean percentage of CD4 cells; decreased mean percentage of CD8 cells; reduced percentage of naive CD4 and CD8 T cells in lymph nodes; increased

10 mean percentage of B cells in peripheral blood; decrease total white blood cells and lymphocyte counts; decreased absolute lymphocyte counts; increased mean absolute monocyte count; increased mean absolute neutrophil count; decreased in mean serum IgA levels; increase in mean serum IgA levels; increase in IgG1 levels; decreased mean serum IgG1 levels; decreased mean serum IgG1, IgG3, IgG2b and IgG2a levels; decreased mean serum IgG2a levels; decreased mean serum IgG2b levels; decreased mean serum IgG3 and IgM levels; increase in mean serum

15 IgG2a levels; increase in mean serum IgG1, IgG2a and IgG3 levels; increase in mean serum IgG3 levels; anemia; decreased red blood cell count, decreased hemoglobin and decreased hematocrit with increased mean red blood cell count; increased mean corpuscular volume; decreased mean corpuscular volume; decreased mean corpuscular hemoglobin; increased red blood cell distribution width; defect in erythropoiesis; increased IgM+ IgD+ and B220hi/CD43- cells in bone marrow; decreased percentage of B220hi/CD43- IgM+ IgD+ cells in bone marrow;

20 increased percentage of TCRB+ cells in Peyer's patches; reduction in naive T cells (especially CD4) in lymph nodes; increased percentage of CD11b+CD11c- cells (monocytes) in spleen; increased percentage of IgM+, CD117+ cells in bone marrow, higher percentage of dead B cells, decreased B cells, increased CD4 and CD8 T cells in lymph; B cells increased in bone marrow and significantly decreased in lymph node; notably decreased CD21hiCD23med B cells in spleen; decrease in Peyer's patch B220+ cells; decreased mean percentages of CD8

25 and natural killer cells with increased mean percentage of B cells; reduced number of TCRB+ CD38+ activated T cells in Peyer's patches; decreased mean percentage of CD4 cells with increased mean percentage of B cells; decreased B220+ CD38low and IgM in Payer's patches; increased mean platelet count; decreased mean platelet count; widespread apoptosis and loss of T lymphocytes in the thymic cortex and depletion of T cells in spleen; increased mean serum IgG2a response to an ovalbumin challenge; decreased to no serum IgG1 and IgG2a

30 response to ovalbumin challenge; increased mean serum IgG1 response to an ovalbumin challenge; decreased mean serum TNF-alpha, MCP-1 and IL-6 responses to LPS challenge; increased mean serum MCP-1 response to a LPS challenge; increased mean serum TNF-alpha response to a LPS challenge; increased mean serum IL-6 response to a LPS challenge; increased skin fibroblast proliferation; decreased skin fibroblast proliferation; increased mean percent of total body fat and total fat mass; increased mean body weight; increased mean body length; increased

35 total tissue mass (TTM); increased lean body mass (LBM); increased femoral bone mineral density (BMD); increased vertebral bone mineral density (BMD); increased bone mineral density (BMD); increased total body volumetric bone mineral density (vBMD); increased bone mineral content (BMC); increased mean femoral midshaft cortical thickness and cross-sectional area; increased mean vertebral trabecular bone volume, number and

connectivity density; decreased mean percent of total body fat and total fat mass; decreased mean body weight; decreased mean body length; decreased total tissue mass (TTM); decreased lean body mass (LBM); decreased femoral bone mineral density (BMD); decreased vertebral bone mineral density (BMD); decreased bone mineral density (BMD); decreased bone mineral content (BMC); decreased bone mineral density index; decreased volumetric bone mineral density (vBMD); decreased mean femoral midshaft cortical thickness and cross-sectional area; decreased mean vertebral trabecular bone volume, number and connectivity density; marked osteopetrosis with increased bone mineralization; chronic inflammation in various tissues; thymic atrophy; systemic histiocytic storage disease affecting macrophages in liver, spleen and mesenteric lymph nodes; reduced liver size; chronic active hepatitis with focal hepatocyte necrosis; fatty changes in the liver; increased intracytoplasmic vacuolization of glycogen in hepatocytes; pancreatic dyserythropoietic anemia (type 1); multifocal neuronal necrosis; diffuse abiotrophy of the cerebellum granule cell layer; multifocal developmental malformation of the brain; hydronephrosis; diffuse alopecia; epidermal hyperkeratosis; hypochromasia and anisocytosis characterized by abnormal erythrocytes (abnormally low hemoglobin and decreased erythropoiesis); growth retardation; development abnormalities; granulocytic hypoplasia of bone marrow; decreased numbers of myeloid granulocytic cell precursors; decreased granulocytopoiesis; no teeth; stunted growth with general reduction in all organ size; myocardial defects with defective structure and arrangement of the cardiac myocytes; cardiomyopathy with condensed eosinophilic sarcoplasm; congestive heart failure; pancreatic islets of Langerhans smaller and distribution of alpha (glycogen) and beta (insulin) cells altered; notable histopathologic alteration in cytoplasm of all cells in the zona fasciculata of the adrenal gland consistent with altered lipid/cholesterol uptake or metabolism (elevated cholesterol and triglycerides); infertility; testicular degeneration; vacuolar degeneration of seminiferous tubules; hypospermia; atrophic testes; ovarian and uterine hypoplasia; mammary gland was represented with just a few ducts; growth retardation with reduced viability; and embryonic lethality.

86. An agent identified by the method of Claim 67.

87. The agent of Claim 86 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

88. The agent of Claim 87, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-

PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250antibody.

89. The agent of Claim 87, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250antibody.

90. A therapeutic agent identified by the method of Claim 67.

91. A method of identifying an agent that modulates the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

- (a) contacting a test agent with a host cell expressing a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide; and
- (b) determining whether the test agent modulates the expression of the PRO69122, PRO204, PRO214,

PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide by the host cell.

92. An agent identified by the method of Claim 91.

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93. The agent of Claim 92 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

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94. The agent of Claim 93, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

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95. The agent of Claim 93, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-

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PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

- 5 96. A method of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:
- 10 (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;
- 15 (b) measuring a physiological characteristic of the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal;
- 20 (d) administering a test agent to the non-human transgenic animal of (a); and
- (e) evaluating the effects of the test agent on the identified condition associated with gene disruption in the non-human transgenic animal.
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97. The method of Claim 96, wherein the condition is a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

35 98. A therapeutic agent identified by the method of Claim 96.

99. The therapeutic agent of Claim 98 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

100. The therapeutic agent of Claim 99, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

101. The therapeutic agent of Claim 99, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

102. A pharmaceutical composition comprising the therapeutic agent of Claim 98.

103. A method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994,

PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject in need of such treatment whom may already have the disorder, or may be prone to have the disorder or may be in whom the disorder is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 94, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

104. The method of Claim 103, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

105. The method of Claim 103, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

106. The method of Claim 103, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

107. The method of Claim 103, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

108. The method of Claim 103, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

109. The method of Claim 103, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

110. The method of Claim 103, wherein the eye abnormality is a retinal abnormality.

111. The method of Claim 103, wherein the eye abnormality is consistent with vision problems or blindness.

112. The method of Claim 110, wherein the retinal abnormality is consistent with retinitis pigmentosa.

113. The method of Claim 110, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

114. The method of Claim 110, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedrich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

115. The method of Claim 103, wherein the eye abnormality is a cataract.

116. The method of Claim 115, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

117. The method of Claim 103, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

118. The method of Claim 103, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e.g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

119. The method of Claim 103, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic

inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

120. The method of Claim 103, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

121. A method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising:

(a) providing a non-human transgenic animal cell culture, each cell of said culture comprising a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide;

(b) administering a test agent to said cell culture; and

(c) determining whether said test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in said cell culture.

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122. The method of Claim 121, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

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123. The method of Claim 121, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

124. The method of Claim 121, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

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125. The method of Claim 121, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

126. The method of Claim 121, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

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127. The method of Claim 121, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

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128. The method of Claim 121, wherein the eye abnormality is a retinal abnormality.

129. The method of Claim 121, wherein the eye abnormality is consistent with vision problems or blindness.

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130. The method of Claim 128, wherein the retinal abnormality is consistent with retinitis pigmentosa.

131. The method of Claim 128, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

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132. The method of Claim 128, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma,

angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

133. The method of Claim 121, wherein the eye abnormality is a cataract.

134. The method of Claim 133, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

135. The method of Claim 121, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

136. The method of Claim 121, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

137. The method of Claim 121, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the

central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

138. The method of Claim 121, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

139. An agent identified by the method of Claim 121.

140. The agent of Claim 139 which is an agonist or antagonist of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide.

141. The agent of Claim 140, wherein the agonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540, anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

142. The agent of Claim 140, wherein the antagonist is an anti-PRO69122, anti-PRO204, anti-PRO214, anti-PRO222, anti-PRO234, anti-PRO265, anti-PRO309, anti-PRO332, anti-PRO342, anti-PRO356, anti-PRO540,

anti-PRO618, anti-PRO944, anti-PRO994, anti-PRO1079, anti-PRO1110, anti-PRO1122, anti-PRO1138, anti-PRO1190, anti-PRO1272, anti-PRO1286, anti-PRO1295, anti-PRO1309, anti-PRO1316, anti-PRO1383, anti-PRO1384, anti-PRO1431, anti-PRO1434, anti-PRO1475, anti-PRO1481, anti-PRO1568, anti-PRO1573, anti-PRO1599, anti-PRO1604, anti-PRO1605, anti-PRO1693, anti-PRO1753, anti-PRO1755, anti-PRO1777, anti-PRO1788, anti-PRO1864, anti-PRO1925, anti-PRO1926, anti-PRO3566, anti-PRO4330, anti-PRO4423, anti-PRO36935, anti-PRO4977, anti-PRO4979, anti-PRO4980, anti-PRO4981, anti-PRO5801, anti-PRO5995, anti-PRO6001, anti-PRO6095, anti-PRO6182, anti-PRO7170, anti-PRO7171, anti-PRO7436, anti-PRO9912, anti-PRO9917, anti-PRO37337, anti-PRO37496, anti-PRO19646, anti-PRO21718, anti-PRO19820, anti-PRO21201, anti-PRO20026, anti-PRO20110, anti-PRO23203 or anti-PRO35250 antibody.

143. A therapeutic agent identified by the method of Claim 121.

144. A method of modulating a phenotype associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already have the phenotype, or may be prone to have the phenotype or may be in whom the phenotype is to be prevented, an effective amount of the agent of Claim 46, or agonists or antagonists thereof, thereby effectively modulating the phenotype.

145. A method of modulating a physiological characteristic associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already exhibit the physiological characteristic, or may be prone to exhibit the physiological characteristic or may be in whom the physiological characteristic is to be prevented, an effective amount of the agent of Claim 52, or agonists or antagonists thereof, thereby effectively modulating the physiological characteristic.

146. A method of modulating a behavior associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a subject whom may already exhibit the behavior, or may be prone to exhibit the behavior or may be in whom the exhibited behavior is to be prevented, an effective amount of the agent of Claim 63, or agonists or antagonists thereof, thereby effectively modulating the behavior.

147. A method of modulating the expression of a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO285, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a host cell expressing said PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, an effective amount of the agent of Claim 92, or agonists or antagonists thereof, thereby effectively modulating the expression of said polypeptide.

148. A method of modulating a condition associated with a disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250

polypeptide, the method comprising administering to a subject whom may have the condition, or may be prone to have the condition or may be in whom the condition is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 98, or agonists or antagonists thereof, thereby effectively modulating the condition.

149. A method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, the method comprising administering to a non-human transgenic animal cell culture, each cell of said culture comprising a disruption of the gene which encodes for a PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 polypeptide, a therapeutically effective amount of the agent of Claim 139, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

FIGURE 1

AAGAGCAGCGGCGAGGCGGCGGTGGTGGCTGAGTCCGTGGTGGCAGAGGCGAAGGCGACA
GCTCTAGGGGTTGGCACCGGCCCCGAGAGGAGGATGCGGGTCCGGATAGGGCTGACGCTG
CTGCTGTGTGCGGTGCTGCTGAGCTTGGCCTCGGCGTCCTCGGATGAAGAAGGCAGCCAG
GATGAATCCTTAGATTCCAAGACTACTTTGACATCAGATGAGTCAGTAAAGGACCACACT
ACTGCAGGCAGAGTAGTTGCTGGTCAAATATTTCTTGATTCAGAAGAATCTGAATTAGAA
TCCTCTATTCAAGAAGAGGAAGACAGCCTCAAGAGCCAAGAGGGGGAGAGTGTACAGAA
GATATCAGCTTTCTAGAGTCTCCAAATCCAGAAAACAAGGACTATGAAGAGCCAAAGAAA
GTACGGAAACCAGCTTTGACCGCCATTGAAGGCACAGCACATGGGGAGCCCTGCCACTTC
CCTTTCTTTTCTTAGATAAGGAGTATGATGAATGTACATCAGATGGGAGGGAAGATGGC
AGACTGTGGTGTGCTACAACCTATGACTACAAAGCAGATGAAAAGTGGGGCTTTTGTGAA
ACTGAAGAAGAGGCTGCTAAGAGACGGCAGATGCAGGAAGCAGAAATGTTGTATCAAAC
GGAATGAAAATCCTTAATGGAAGCAATAAGAAAAGCCAAAAAGAGAAGCATATCGGTAT
CTCCAAAAGGCAGCAAGCATGAACCATAACCAAGCCCTGGAGAGAGTGTATATGCTCTT
TTATTTGGTGTATTACTTGCCACAGAATATCCAGGCAGCGAGAGAGATGTTTGAGAAGCTG
ACTGAGGAAGGCTCTCCCAAGGGACAGACTGCTCTTGGCTTTCTGTATGCCTCTGGACTT
GGTGTTAATTCAGTCAAGGCAAAGGCTCTTGTATATTATACATTTGGAGCTCTTGGGGGC
AATCTAATAGCCCATGTTTGGGTTACAGATACTGGGCTGGCATCGGCGTCCTCCAG
AGTTGTGAATCTGCCCTGACTCACTATCGTCTTGTGTTGCAATCATGTTGCTAGTGATATC
TCGCTAACAGGAGGCTCAGTAGTACAGAGAATACGGCTGCCTGATGAAGTGAAAAATCCA
GGAATGAACAGTGAATGCTAGAAGAAGATTTGATTCAATATTACCAGTTCCTAGCTGAA
AAAGGTGATGTACAAGCACAGGTTGGTCTTGGACAACTGCACCTGCACGGAGGGCGTGGA
GTAGAACAGAATCATCAGAGAGCATTTGACTACTTCAATTTAGCAGCAAATGCTGGCAAT
TCACATGCCATGGCCTTTTGGGAAAGATGTATTGGAAGGAAGTGACATTGTACCTCAG
AGTAATGAGACAGCTCTCCACTACTTTAAGAAAGCTGCTGACATGGGCAACCCAGTTGGA
CAGAGTGGGCTTGAATGGCCTACCTCTATGGGAGAGGAGTTCAGTTAATTATGATCTA
GCCCTTAAGTATTTCCAGAAAGCTGCTGAACAAGGCTGGGTGGATGGGCAGCTACAGCTT
GGTTCCATGTACTATAATGGCATTGGAGTCAAGAGAGATTATAAACAGGCCTTGAAGTAT
TTTAATTTAGCTTCTCAGGGAGGCCATATCTTGGCTTTCTATAACCTAGCTCAGATGCAT
GCCAGTGGCACCGCGTGATGCGATCATGTACACTGCAGTGGAGTTGTTTAAGAAATGTA
TGTGAACGAGGCCGTTGGTCTGAAAGGCTTATGACTGCCTATAACAGCTATAAAGATGGC
GATTACAATGCTGCAGTGATCCAGTACCTCCTCTGGCTGAACAGGGCTATGAAGTGGCA
CAAAGCAATGCAGCCTTTATTCTTGATCAGAGAGAAGCAAGCATTGTAGGTGAGAATGAA
ACTTATCCCAGAGCTTTGCTACATTGGAACAGGGCCGCCTCTCAAGGCTATACTGTGGCT
AGAATTAAGCTCGGAGACTACCATTTCTATGGGTTTGGCACCGATGTAGATTATGAACT
GCATTTATTATTACCGTCTGGCTTCTGAGCAGCAACACAGTGCAAGCTATGTTTAAT
CTGGGATATATGCATGAGAAAGGACTGGGCATTAAACAGGATATTACCTTGCGAAACGT
TTTTATGACATGGCAGCTGAAGCCAGCCAGATGCACAAGTCCAGTCTTCTAGCCCTC
TGCAAATTGGGCGTCGTCTATTTCTGTCAGTACATACGGGAAACAAACATTTCGAGATATG
TTCACCCAACTTGATATGGACCAGCTTTTGGGACCTGAGTGGGACCTTTACCTCATGACC
ATCATTTGCGCTGCTGTTGGGAACAGTCATAGCTTACAGGCAAAGGCAGCACCAAGACATG
CCTGCACCCAGGCCTCCAGGGCCACGGCCAGCTCCACCCAGCAGGAGGGGCCACCAGAG

FIGURE 1 Continued

CAGCAGCCACCACAGTAATAGGCACTGGGTCCAGCCTTGATCAGTGACAGCGAAGGAAGT
TATCTGCTGGGAACACTTGCATTTGATTTAGGACCTTGGATCAGTGGTCACCTCCCAGAA
GAGGCACGGCACAAGGAAGCATTGAATTCCTAAAGCTGCTTAGAATCTGATGCCTTTATT
TTCAGGGATAAGTAACTCTTACCTAAACTGAGCTGAATGTTTGTTCAGTGCCATATGGA
ATAACAACTTTTTCAGTGGCTTTTTTTTTTCTTTCTGGAACATATGTGAGACACTCAGAG
TAATGTCTACTGTATCCAGCTATCTTTCTGGATCCTTTTGGTCATTATTTTCAGTGTGCA
TAAGTTCTTAATGTCAACCATCTTTAAGGTATTGTGCATCGACACTAAAACTGATCAGT
GTAAAAAGGAAAACCCAGTTGCAAGTTTAAACGTGTTGAAAGTCTGAAAATAGAACTTG
CCTTTTAAGTTAAAAAAGCTATCTTGAAAATGTTTGGAACTGCGATAACTGA
GAACTCTTACCAGTCCACATGCAATTAGACATATTCAGCATATTTGTTATTTTAAAGG
GAGGGTTGGGAGGTTTCTTATTTGGTGATTGTTCACACGGTATACCATACTCCTCTCCTTCA
AAGAATGAAAGGCCCTTGTTAAGGAGTTTTTTGTGAGCTTTACTTCTTTGGAATGGAATAT
ACTTATGCAAAACCTTGTGAACTGACTCCTTGCACTAACGCGAGTTTGCCCCACCTACTC
TGTAATTTGCTTGTTGTTTGAATATACAGAGCCTTGATCCAGAAGCCAGAGGATGGAC
TAAGTGGGAGAAATTAGAAAACAAAACGAACCTCTGGTTGGGGTACTACGATCACAGACAC
AGACATACTTTTCCTAAAGTTGAAGCATTGTGCCAGGATTATTTTACTTTGCATTTT
CTTTTGACAAAGAACACATCACCATTTCTTTTGACAAAGAACACATCACC

FIGURE 2

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><Tue Dec 4 13:44:42 PST 2001 DNA284870 [min]
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA284870
><subunit 1 of 1, 794 aa, 1 stop
><MW: 88723, pI: 5.33, NX(S/T): 5
MRVRIGLTLLLCVLLSLASASSDEEGSQDESLSKTTLTSDSVKDHTTAGRVVAGQIF
LDSESESELESSIQEEEDSLKSQEGESVTEDISFLESPNPENKDYEEPKKVRKPALTAIEG
TAHGEPCHFPPFLFLDKEYDECTSDGREDGRLWCATTYDYKADEKKGFCETEEEAARRQM
QEAEVMVYQTGMKILNGSNKKSQKREAYRYLQKAASMNHTKALERVSYALLFGDYLPQNIQ
AAREMFEEKLTEEGSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLI AHMVLGYR
YWAGIGVLQSCESALTHYRLVANHVASDISLTGGSVVQRI RLPDEVENPGMNSGML EEDL
IQYYQFLAEKGDVQAQVGLGQLHLHGGRGVEQNHQRAFDYFNLAANAGNSHAMAF LGKMY
SEGSDIVPQSNETALHYFKKAADMGNPVGQSGLGMAYLYGRGVQVNYDLALKYFQKAAEQ
GWVDGQLQLGSMYYNGIGVKRDYKQALKYFNLASQGGHILAFYNLAQMHASGTGVMRSCH
TAVELFKNVCERGRWSERLMTAYNSYKGDYNAAVIQYLLLAEQGYEVAQSNAAFILDQR
EASIVGENETYPRALLHWNRAASQGYTVARIKLG DYHFYGF GTD VDYETA FIHYRLASEQ
QHSAQAMFNLGYMHEKGLGIKQDIHLAKRFYDMAAEASPD AQVPVFLALCKLGVVYFLQY
IRETNIRDMFTQLDMDQLLGPWDLYLMTI IALLLGTVIAYRQRQH QDMPAPRPPGPRPA
PPQQEGPPEQQPPQ
```

FIGURE 3

TGCCGGGCTGCGGGGCGCCTTGACTCTCCCTCCACCCTGCCTCCTCGGGCTCCACTCGTCTGCCCCTGACTCC
CGTCTCCTCCTGTCTCCGGCTTCCCAGAGCTCCCTCCTTATGGCAGCAGCTTCCCGCGTCTCCGGCGCAGCTT
CTCAGCGGACGACCCCTCTCGCTCCGGGGCTGAGCCAGTCCCTGGATGTTGCTGAAACTCTCGAGATCATGCGC
GGGTTTGGCTGCTGCTTCCCCGCCGGGTGCCACTGCCACCGCCGCCCTCTGCTGCCGCCGTCCGCGGGATGC
TCAGTAGCCCGCTGCCCCGGCCCCCGCATCCTGTGTTCCCTCGGAAGCCGTTTGCTGCTGCAGAGTTGCACGAAC
TAGTCATGGTGTGTGGGAGTCCCCGCGCAGTGCAGCAGCTGGACACTTTGCGAGGGCTTTTGCTGGCTGCTG
CTGTGCCCCGTCTATGCTACTCATCGTAGCCCGCCCGGTGAAGCTCGCTGCTTTCCCTACCTCCTTAAGTGACTG
CCAAACGCCCACCGGCTGGAATTGCTCTGGTTATGATGACAGAGAAAATGATCTCTTCTCTGTGACACCAACA
CCTGTAAATTTGATGGGGAATGTTAAGAATTGGAGACACTGTGACTTGCGTCTGTCAAGTGCAACAAT
GACTATGTGCCTGTGTGTGGCTCCAATGGGGAGAGCTACCAGAATGAGTGTTACCTGCGACAGGCTGCATGCAA
ACAGCAGAGTGAGATACTTGTGGTGTGAGAAGGATCATGTGCCACAGATGCAGGATCAGGATCTGGAGATGGAG
TCCATGAAGGCTCTGGAGAACTAGTCAAAAGGAGACATCCACCTGTGATATTTGCCAGTTTGGTGCAGAAATGT
GACGAAGATGCCGAGGATGTCTGGTGTGTGTGTAATATTGACTGTTCTCAAACCAACTTCAATCCCCCTCTGCGC
TTCTGATGGGAAATCTTATGATAATGCATGCCAAATCAAAGAAGCATCGTGTGAGAAACAGGAGAAAATGAAG
TCATGTCTTTGGTTCGATGTCAAGATAACACAACACTACAATACTAAGTCTGAAGATGGGCATTATGCAAGAACA
GATTATGCAGAGAATGCTAACAATTAGAAGAAAGTGCCAGAGAACACCACATACCTTGTCGGGAACATTACAA
TGGCTTCTGCATGCATGGGAAGTGTGAGCATTTCTATCAATATGCAGGAGCCATCTTGCCAGGTGTGATGCTGGTT
ATACTGGACAACACTGTGAAAAAAGGACTACAGTGTTCTATACGTTGTTCCCGGTCTGTACGATTTTCAGTAT
GTCTTAATCGCAGCTGTGATTGGAACAATTGAGATTGCTGTGTCATCTGTGTGGTGGTCTCTGCATCACAAGGAA
ATGCCCCAGAAGCAACAGAAATTCACAGACAGAAGCAAAATACAGGGCACTACAGTTTCAGACAATACAACAAGAG
CGTCCACGAGGTTAATCTAAAGGGAGCATGTTTCACAGTGGCTGGACTACCGAGAGCTTGGACTACACAATACA
GTATTATAGACAAAAGAATAAGACAAGAGATCTACACATGTTGCCTTGCAATTTGTGGTAATCTACACCAATGAA
AACATGTACTACAGCTATATTTGATTATGTATGGATATATTTGAAATAGTATACATTGCTTGTATGTTTTTCT
GTAATGTAAATAAACTATTTATATCACACAATATAGTTTTTCTTTCCCATGTATTTGTATATATAATAAATA
CTCAGTGATGAG

FIGURE 4

MVLWESPRQCSSWTLCEGFCWLLLLPVMLLIVARPVKLAAFPTSLSDCQTPTGWNC SGY
DDRENDLFLCDTNTCKFDGECLRIGDTVTCVCQFKCNNDYVPVCGSNGESYQNECYLRQ
AACKQQSEILVVSEGSCATDAGSGSGDGVHEGSGETSQKETSTCDICQFGAECDEDAED
VWCVCNIDCSQTNFNPLCASDGKSYDNACQIKEASCQKQEKIEVMSLGRCQDNTTTT TK
SEDGHYARTDYAENANKLEESAREHHIPCPEHYNGFCMHGKCEHSINMQEPSRCRDAGY
TGQHCEKKDYSVLYVVP GPVRFQYVLIAAVIGTIQIAVICVVLCITRKCPRSNRIHRQ
KQNTGHYSSDNTTTRASTRLI

FIGURE 5

CGGACGCGTGGGCGGACGCGTGGGCGGCCACGGCGCCCGGGCTGGGGCGGTCGCTTCT
TCCTTCTCCGTGGCCTACGAGGGTCCCCAGCCTGGGTAAAGATGGCCCCATGGCCCCCGAA
GGGCTAGTCCCAGCTGTGCTCTGGGGCCTCAGCCTCTTCCTCAACCTCCCAGGACCTATC
TGGCTCCAGCCCTCTCCACCTCCCCAGTCTTCTCCCCCGCCTCAGCCCCATCCGTGTCATA
CCTGCCGGGGACTGGTTGACAGCTTTAACAAGGGCCTGGAGAGAACCATCCGGGACAACCTT
TGGAGGTGGAACACTGCCTGGGAGGAAGAGAATTTGTCCAAATACAAAGACAGTGAGACC
CGCCTGGTAGAGGTGCTGGAGGGTGTGTGCAGCAAGTCAGACTTCGAGTGCCACCGCCTGC
TGGAGCTGAGTGAGGAGCTGGTGGAGAGCTGGTGGTTTCAACAAGCAGCAGGAGGCCCGGA
CCTCTTCCAGTGGCTGTGCTCAGATTCCCTGAAGCTCTGCTGCCCCGCAGGCACCTTCGGG
CCCTCCTGCCTTCCCTGTCTGGGGGAACAGAGAGGCCCTGCGGTGGCTACGGGCAGTGTG
AAGGAGAAGGGACACGAGGGGGCAGCGGGCACTGTGACTGCCAAGCCGGCTACGGGGGTGA
GGCCTGTGGCCAGTGTGGCCTTGGCTACTTTGAGGCAGAACGCAACGCCAGCCATCTGGTA
TGTTGCGCTTGTTTTGGCCCCCTGTGCCCCGATGCTCAGGACCTGAGGAATCAAACCTGTTTGC
AATGCAAGAAGGGCTGGGGCCCTGCATCACCTCAAGTGTGTAGACATTGATGAGTGTGGCAC
AGAGGGAGCCAACTGTGGAGCTGACCAATTCTGCGTGAACACTGAGGGCTCCTATGAGTGC
CGAGACTGTGCCAAGGCCTGCCTAGGCTGCATGGGGGCAGGGCCAGGTGCTGTAAGAAGT
GTAGCCCTGGCTATCAGCAGGTGGGCTCCAAGTGTCTCGATGTGGATGAGTGTGAGACAGA
GGTGTGTCCGGGAGAGAAACAAGCAGTGTGAAAACACCGAGGGCGGTTATCGCTGCATCTGT
GCCCAGGGCTACAAGCAGATGGAAGGCATCTGTGTGAAGGAGCAGATCCCAGAGTCAGCAG
GCTTCTTCTCAGAGATGACAGAAGACGAGTTGGTGGTGCTGCAGCAGATGTTCTTTGGCAT
CATCATCTGTGCACTGGCCACGCTGGCTGCTAAGGGCGACTTGGTGTTCACCGCCATCTTC
ATTGGGGCTGTGGCGGCCATGACTGGCTACTGGTTGTCAGAGCGCAGTGACCGTGTGCTGG
AGGGCTTCATCAAGGGCAGATAATCGCGGCCACCACCTGTAGGACCTCCTCCCACCCACGC
TGCCCCCAGAGCTTGGGCTGCCCTCCTGCTGGACACTCAGGACAGCTTGGTTTATTTTTGA
GAGTGGGGTAAGCACCCCTACCTGCCTTACAGAGCAGCCCAGGTACCCAGGCCCGGGCAGA
CAAGGCCCCCTGGGGTAAAAAGTAGCCCTGAAGGTGGATAACCATGAGCTCTTCACCTGGCGG
GGACTGGCAGGCTTCACAATGTGTGAATTTCAAAAAGTTTTTCTTAATGGTGGCTGCTAGA
GCTTTGGCCCCCTGCTTAGGATTAGGTGGTCTCACAGGGGTGGGGCCATCACAGCTCCCTC
CTGCCAGCTGCATGCTGCCAGTTCCTGTTCTGTGTTACCACATCCCCACACCCATTGCC
ACTTATTTATTCATCTCAGGAAATAAAGAAAGGTCTTGAAAGTTAAAAAAAAAAAAAAAAA
AAAAAAA

FIGURE 6

MAPWPPKGLVPAVLWGLSLFLNLPGPWLQPSPPPQSSPPPQPHPCHTCRGLVDSFNKGLE
RTIRDNFGGGNTAWEEENLSKYKDSETRLVEVLEGVCSKSDFECHRLLELSEELVESWWFH
KQQEAPDLFQWLCSDSLKLCPPAGTFGPSCLPCPGGTERPCGGYGQCEGEGTRGGSGHCDC
QAGYGGEACGQCGLGYFEAERNASHLVCSACFGPCARCSGPESNCLQCKKGWALHHLKCV
DIDECGTEGANCGADQFCVNTEGSYECRDCAKACLGCMGAGPGRCKKCSPGYQQVGSKCLD
VDECETEVCPCGENKQCENTEGGYRCICAEGYKQMEGICVKEQIPESAGFFSEMTEDELVVL
QQMFFGIIICALATLAAKGDVFTAFIFIGAVAAMTGYWLSERSDRVLEGFIKGR

Signal sequence:

amino acids 1-29

Transmembrane domain:

amino acids 372-395

N-glycosylation site.

amino acids 79-83, 205-209

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 290-294

Casein kinase II phosphorylation site.

amino acids 63-67, 73-77, 99-103, 101-105, 222-226, 359-263

N-myristoylation site.

amino acids 8-14, 51-57, 59-65, 69-75, 70-76, 167-173, 173-179,
177-183, 188-194, 250-256, 253-259, 267-273, 280-286, 283-289,
326-332, 372-378, 395-401

Aspartic acid and asparagine hydroxylation site.

amino acids 321-333

EGF-like domain cysteine pattern signature.

amino acids 181-193

FIGURE 7

CCCACGCGTCCGGTCTCGCTCGCTCGCGCAGCGGCGGCAGCAGAGGTCGCGCACAGATGCCG
GGTTAGACTGGCGGGGGGAGGAGGCGGAGGAGGGAAGGAAGCTGCATGCATGAGACCCACA
GACTCTTGCAAGCTGGATGCCCTCTGTGGATGAAAGATGTATCATGGAATGAACCCGAGCA
ATGGAGATGGATTTCTAGAGCAGCAGCAGCAGCAGCAACCTCAGTCCCCCAGAGACT
CTTGGCCGTGATCCTGTGGTTTCAGCTGGCGCTGTGCTTCGGCCCTGCACAGCTCACGGGC
GGGTTGATGACCTTCAAGTGTGTGCTGACCCCGGCATTCCCGAGAATGGCTTCAGGACCC
CCAGCGGAGGGGTTTTCTTTGAAGGCTCTGTAGCCCGATTTCACTGCCAAGACGGATTCAA
GCTGAAGGGCGCTACAAAGAGACTGTGTTTGAAGCATTTTAATGGAACCCTAGGCTGGATC
CCAAGTGATAATTCCATCTGTGTGCAAGAAGATTGCCGTATCCCTCAAATCGAAGATGCTG
AGATTCATAACAAGACATATAGACATGGAGAGAAGCTAATCATCACTTGTTCATGAAGGATT
CAAGATCCGGTACCCCGACCTACACAATATGGTTTCATTATGTGCGGATGATGGAACGTGG
AATAATCTGCCCATCTGTCAAGGCTGCCTGAGACCTCTAGCCTCTTCTAATGGCTATGTAA
ACATCTCTGAGCTCCAGACCTCCTTCCCGGTGGGGACTGTGATCTCCTATCGCTGCTTTCC
CGGATTTAAACTTGATGGGTCTGCGTATCTTGAGTGCTTACAAAACCTTATCTGGTCGTCC
AGCCCCCCCCGGTGCTTGCTCTGGAAGCCCAAGTCTGTCCACTACCTCCAATGGTGAGTC
ACGGAGATTTCTGCTGCCACCCGCGGCCTTGTGAGCGCTACAACCACGGAACGTGTGGTGGA
GTTTTACTGCGATCCTGGCTACAGCCTCACCAGCGACTACAAGTACATCACCTGCCAGTAT
GGAGAGTGGTTTCCTTCTTATCAAGTCTACTGCATCAAATCAGAGCAAACGTGGCCCAGCA
CCCATGAGACCCTCCTGACCACGTGGAAGATTGTGGCGTTACGGCAACCAGTGTGCTGCT
GGTGCTGCTGCTCGTCATCCTGGCCAGGATGTTCCAGACCAAGTTCAGGGCCCACTTTCCC
CCCAGGGGGCCTCCCCGGAGTTCCAGCAGTGACCCTGACTTTGTGGTGGTAGACGGCGTGC
CCGTCATGCTCCCGTCCTATGACGAAGCTGTGAGTGGCGGCTTGAGTGCCTTAGGCCCCGG
GTACATGGCCTCTGTGGGCCAGGGCTGCCCCCTTACCCGTGGACGACCAGAGCCCCCAGCA
TACCCCGGCTCAGGGGACACGGACACAGGCCAGGGGAGTCAGAAACCTGTGACAGCGTCT
CAGGCTCTTCTGAGCTGCTCCAAAGTCTGTATTACCTCCCAGGTGCCAAGAGAGCACCCA
CCCTGCTTCGGACAACCTGACATAATTGCCAGCACGGCAGAGGAGGTGGCATCCACCAGC
CCAGGCATCCATCATGCCCACTGGGTGTTGTTTCTTAAGAACTGATTGATTAAAAAATTTCT
CCAAAGTGTCCTGAAGTGTCTCTTCAAATACATGTTGATCTGTGGAGTTGATTCTTTCTCT
TCTCTTGGTTTTAGACAAATGTAAACAAAGCTCTGATCCTTAAAATTGCTATGCTGATAGA
GTGGTGAGGGCTGGAAGCTTGATCAAGTCCTGTTTCTTCTTGACACAGACTGATTAAAAAT
TAAAGNAAAAAA

FIGURE 8

MYHGMNPSNGDGFLEQQQQQQQPQSPQRLIAVILWFQLALCFGPAQLTGGFDDLQVCADPG
IPENGFRTPSGGVFFEGSVARFHCQDGFKLKGATKRLCLKHFNGTLGWIPSDNSICVQEDC
RIPQIEDAEIHNKTYRHGEKLIITCHEGFKIRYPDLHNMVSLCRDDGTWNNLPICQGCLRP
LASSNGYVNISELQTSFPVGTVISYRCFPGFKLDGSAYLECLQNLIWSSSPPRCLALEAQV
CPLPPMVSHGDFVCHPRPCERYNHGTVVEFYCDPGYSLTSDYKYITCQYGEWFPSYQVYCI
KSEQTWPSTHETLLTTWKIVAFTATSVLLVLLLVLARMFQTKFAHFPPRGPPRSSSSDP
DFVVVDGVPVMLPSYDEAVSGGLSALGPGYMASVGQGCPLPVDDQSPPAYPGSGD TDTGPG
ESETCDSVSGSSELLQSLYSPPRCQESTHPASDNPDIIASTAEVASTSPGIHHAHWLFLRN

Signal sequence:

amino acids 1-41

Transmembrane domain:

amino acids 325-344

N-glycosylation site.

amino acids 104-108, 134-138, 192-196

Casein kinase II phosphorylation site.amino acids 8-12, 146-150, 252-256, 270-274, 313-317, 362-366,
364-368, 380-384, 467-471, 468-472**N-myristoylation site.**amino acids 4-10, 61-67, 169-175, 203-209, 387-393, 418-424,
478-484**Prokaryotic membrane lipoprotein lipid attachment site.**

amino acids 394-405

FIGURE 9

CCCACGCGTCCGCTCCGCGCCCTCCCCCGCCTCCCGTGCGGTCCGTCCGTGGCCTAGAG
ATGCTGCTGCCGCGGTTCAGTTGTGCGGCACGCCTCTGCCCGCCAGCCCGCTCCACCGCC
GTAGCGCCCGAGTGTCGGGGGGCGCACCCGAGTCGGGGCCATGAGGCCGGAACCGCGCTAC
AGGCCGTGCTGCTGGCCGTGCTGCTGGTGGGGCTGCGGGCCGCGACGGGTGCGCTGCTGAG
TGCCTCGGATTTGGACCTCAGAGGAGGGCAGCCAGTCTGCCGGGAGGGACACAGAGGCCT
TGTTATAAAGTCATTTACTTCCATGATACTTCTCGAAGACTGAACTTTGAGGAAGCCAAAG
AAGCCTGCAGGAGGGATGGAGGCCAGCTAGTCAGCATCGAGTCTGAAGATGAACAGAACT
GATAGAAAAGTTTCATTGAAAACCTCTTGCCATCTGATGGTGACTTCTGGATTGGGCTCAGG
AGGCGTGAGGAGAAACAAAGCAATAGCACAGCCTGCCAGGACCTTTATGCTTGGA CTGATG
GCAGCATATCACAATTTAGGAACTGGTATGTGGATGAGCCGTCCTGCGGCAGCGAGGTCTG
CGTGGTCATGTACCATCAGCCATCGGCACCCGCTGGCATCGGAGGCCCTACATGTTCCAG
TGGAATGATGACCGGTGCAACATGAAGAACAATTTCATTTGCAAATATTCTGATGAGAAAC
CAGCAGTTCCTTCTAGAGAAGCTGAAGGTGAGGAAACAGAGCTGACAACACCTGTACTTCC
AGAAGAAACACAGGAAGAAGATGCCAAAAAACATTTAAAGAAAGTAGAGAAGCTGCCTTG
AATCTGGCCTACATCCTAATCCCCAGCATTCCCCTTCTCCTCCTCCTTGTGGTCACCACAG
TTGTATGTTGGGTTTGGATCTGTAGAAAAAGAAAACGGGAGCAGCCAGACCCTAGCACAAA
GAAGCAACACACCATCTGGCCCTCTCCTCACCAGGGAAACAGCCCGGACCTAGAGGTCTAC
AATGTCATAAGAAAACAAAGCGAAGCTGACTTAGCTGAGACCCGGCCAGACCTGAAGAATA
TTTCATTCCGAGTGTTTCGGGAGAAGCCACTCCCGATGACATGTCTTGTGACTATGACAA
CATGGCTGTGAACCCATCAGAAAGTGGGTTTGTGACTCTGGTGAGCGTGAGAGTGGATTT
GTGACCAATGACATTTATGAGTTCTCCCCAGACCAAATGGGGAGGAGTAAGGAGTCTGGAT
GGGTGGAATGAAATATATGGTTATTAGGACATATAAAAACTGAACTGACAACAATGG
AAAAGAAATGATAAGCAAAATCCTCTTATTTTCTATAAGGAAAATACACAGAAGGTCTATG
AACAGCTTAGATCAGGTCTGTGGATGAGCATGTGGTCCCCACGACCTCCTGTTGGACCC
CCACGTTTTGGCTGTATCCTTTATCCCAGCCAGTCATCCAGCTCGACCTTATGAGAAGGTA
CCTTGCCAGGTCTGGCACATAGTAGAGTCTCAATAAATGTCACTTGGTTGGTTGTATCTA
ACTTTTAAGGGACAGAGCTTTACCTGGCAGTGATAAAGATGGGCTGTGGAGCTTGAAAAAC
CACCTCTGTTTTCTTGCTCTATACAGCAGCACATATTATCATACAGACAGAAAATCCAGA
ATCTTTTCAAAGCCACATATGGTAGCACAGGTTGGCCTGTGCATCGGCAATTCTCATATC
TGTTTTTTTTCAAAGAATAAAATCAAATAAAGAGCAGGAAAAAAAAA

FIGURE 10

MRPGTALQAVLLAVLLVGLRAATGRLLSASDLDLRGGQPVCRRGGTQRPCYKVIYFHDTSRR
LNFEEAKEACRRDGGQLVSI ESEDEQK LIEKF IENLLPSDGD F WIGLRRREEKQSNSTACQ
· DLYAWTDGSI SQFRNWYVDEPSCGSEVCVVMYHQPSAPAGIGGPYMFQWND DRCNMKNFI
CKYSDEKPAVPSREAEGEETELTTPVLPEETQEEDAKKTFKESREAAALNLAYILIPSIPLL
LLLVTTVVCWVWICRKRKREQPD PSTKKQHTIWPSPHQGNSPDLEVYNVIRKQSEADLAE
TRPDLKNISFRVCSGEATPDDMSCDYDNMAVNPSESGFVTLVSVESGFVTNDIYEFSPDQM
GRSKESGWVENEIYGY

Signal sequence:

amino acids 1-21

Transmembrane domain:

amino acids 235-254

N-glycosylation site.

amino acids 117-121, 312-316

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 296-300

Casein kinase II phosphorylation site.

amino acids 28-32, 30-34, 83-87, 100-104, 214-218, 222-226,
299-303, 306-310, 323-327

N-myristoylation site.

amino acids 18-24, 37-43, 76-82, 146-152

FIGURE 11

ACTTGCCATCACCTGTTGCCAGTGTGGAAAAATTCTCCCTGTTGAATTTTTTGCACATGGA
GGACAGCAGCAAAGAGGGCAACACAGGCTGATAAGACCAGAGACAGCAGGGAGATTATTTT
ACCATACGCCCTCAGGACGTTCCCTCTAGCTGGAGTTCTGGACTTCAACAGAACCCCATCC
AGTCATTTTGATTTTGCTGTTTATTTTTTTTTTCTTTTTCTTTTTCCCACCACATTGTATT
TTATTTCCGTACTTCAGAAATGGGCCTACAGACCACAAAGTGGCCCAGCCATGGGGCTTTT
TTCCTGAAGTCTTGGCTTATCATTTCCTGGGGCTCTACTCACAGGTGTCCAACTCCTGG
CCTGCCCTAGTGTGTGCCGCTGCGACAGGAACCTTGTCTACTGTAATGAGCGAAGCTTGAC
CTCAGTGCCTCTTGGGATCCCGGAGGGCGTAACCGTACTCTACCTCCACAACAACCAAATT
AATAATGCTGGATTTCTGCAGAACTGCACAATGTACAGTCGGTGCACACGGTCTACCTGT
ATGGCAACCAACTGGACGAATTCCCCATGAACCTTCCCAAGAATGTCAGAGTTCTCCATTT
GCAGGAAAAACAATATTCAGACCATTTACGGGCTGCTCTTGCCCAGCTCTTGAAGCTTGAA
GAGCTGCACCTGGATGACAACTCCATATCCACAGTGGGGGTGGAAGACGGGGCCTTCCGGG
AGGCTATTAGCCTCAAATTGTTGTTTTTGTCTAAGAATCACCTGAGCAGTGTGCCCTGTTGG
GCTTCCTGTGGACTTGCAAGAGCTGAGAGTGGATGAAAATCGAATTGCTGTCTATCCGAC
ATGGCCTTCCAGAATCTCACGAGCTTGGAGCGTCTTATTGTGGACGGGAACCTCCTGACCA
ACAAGGGTATCGCCGAGGGCACCTTCAGCCATCTCACCAAGCTCAAGGAATTTTCAATTGT
ACGTAATTGCTGTCCCACCCTCCTCCCGATCTCCCAGGTACGCATCTGATCAGGCTCTAT
TTGCAGGACAACCAGATAAACCACATTCTTTGACAGCCTTCTCAAATCTGCGTAAGCTGG
AACGGCTGGATATATCCAACAACCAACTGCGGATGCTGACTCAAGGGGTTTTTGATAATCT
CTCCAACCTGAAGCAGCTCACTGCTCGGAATAACCTTGGTTTTGTGACTGCAGTATTAA
TGGGTCACAGAATGGCTCAAATATATCCCTTCATCTCTCAACGTGCGGGGTTTCATGTGCC
AAGGTCTGAACAAGTCCGGGGGATGGCCGTGAGGAATTAAATATGAATCTTTTGTCTGT
TCCCACCACGACCCCCGGCCTGCCTCTCTTACCCCAGCCCCAAGTACAGCTTCTCCGACC
ACTCAGCCTCCCACCCTCTCTATTCCAAACCCTAGCAGAAGCTACACGCCTCCAACTCCTA
CCACATCGAACTTCCCACGATTCTGACTGGGATGGCAGAGAAAGAGTGACCCACCTAT
TTCTGAACGGATCCAGCTCTCTATCCATTTTGTGAATGATACTTCCATTCAAGTCAGCTGG
CTCTCTCTTTCACCGTGATGGCATAAACTCACATGGGTGAAAATGGGGCCACAGTTTAG
TAGGGGGCATCGTTCAGGAGCGCATAGTCAGCGGTGAGAAGCAACACCTGAGCCTGGTTAA
CTTAGAGCCCCGATCCACCTATCGGATTTGTTTAGTGCCACTGGATGCTTTTAACTACCGC
GCGGTAGAAGACACCATTGTTCAGAGGCCACCACCCATGCCTCCTATCTGAACAACGGCA
GCAACACAGCGTCCAGCCATGAGCAGACGACGTCCACAGCATGGGCTCCCCCTTTCTGCT
GGCGGGCTTGATCGGGGGCGCGGTGATATTTGTGCTGGTGGTCTTGCTCAGCGTCTTTTGC
TGGCATATGCACAAAAGGGGCGCTACACCTCCAGAAGTGGAAATACAACGGGGCCGGC
GGAAAGATGATTATTGCGAGGCAGGCACCAAGAAGGACAACCTCCATCCTGGAGATGACAGA
AACCAGTTTTCAGATCGTCTCCTTAAATAACGATCAACTCCTTAAAGGAGATTTTCAGACTG

FIGURE 11 Continued

CAGCCCATTACACCCCAAATGGGGGCATTAATTACACAGACTGCCATATCCCCAACAACA
TGC GATACTGCAACAGCAGCGTGCCAGACCTGGAGCACTGCCATACGTGACAGCCAGAGGC
CCAGCGTTATCAAGGCGGACAATTAGACTCTTGAGAACACACTCGTGTGTGCACATAAAGA
CACGCAGATTACATTTGATAAATGTTACACAGATGCATTTGTGCATTTGAATACTCTGTAA
TTTATACGGTGTACTATATAATGGGATTTAAAAAAGTGCTATCTTTTCTATTTCAAGTTA
ATTACAAACAGTTTTGTAACTCTTGCTTTTTTAAATCTT

FIGURE 12

MGLQTTKWPSHGAFFLKSWLIISLGLYSQVSKLLACPSVCRCDRNFVYCNERSLTSVPLGI
PEGVTVLYLHNNQINNAGFPAELHNVQSVHTVYLYGNQLDEFFMNLPKNVRVLHLQENNIQ
TISRALAQLLKLEELHLDNSISTVGVEDGAFREAI SLKLLFSLKNHLSSVPVGLPVDLQ
ELRV DENRIAVISDMAFQNLTSLERLIVDGNLLTNKGIAEGTFSHLTKLKEFSIVRNSLSH
PPPDLPGTHLIRLYLQDNQINHIPLTAFSNLRKLERLDISNNQLRMLTQGVFDNLSNLKQL
TARNNPWFCDCSI KWVTEWLKYIPSSLNVRGFMCGPEQVRGMAVRELNMMNLLSCPTTTTPG
LPLFTPAPSTASPTTQPPTLSIPNPSRSYTPPTPTTSKLPTIPDWDGRERVTPPISERIQL
SIHFVNDTSIQVSWLSLFTVMAYKLTWVKMGHSLVGGIVQERIVSGEKQHLSLVNLEPRST
YRICLVPLDAFNRYRAVEDTICSEATTHASYLNNGSNTASSHEQTTSHSMGSPFLLAGLIGG
AVIFVLVLLSVFCWHMHKKGRYTSQKWYNRGRRKDDYCEAGTKKDNSILEMTETSFQIV
SLNNDQLLKGD FRLQPIYTPNGGINYTDCHIPNNMRYCNSSVPDLEHCHT

Signal peptide:

amino acids 1-42

Transmembrane domain:

amino acids 542-561

N-glycosylation site:

amino acids 202-206, 298-302, 433-437, 521-525, 635-639, 649-653

Casein kinase II phosphorylation site.

amino acids 204-208, 407-411, 527-531, 593-597, 598-602, 651-655

Tyrosine kinase phosphorylation site.

amino acids 319-328

N-myristoylation site.

amino acids 2-8, 60-66, 149-155, 213-219, 220-226, 294-300,
522-528, 545-551, 633-639

Amidation site.

amino acids 581-585

Leucine zipper pattern.

amino acids 164-186

Phospholipase A2 aspartic acid active site.

amino acids 39-50

FIGURE 13

TAGGAGGTCCCCGGGTGCGCGCGGCAGCGGGGAAGCATGACTGCTGTGGGCCGAA
GGTGCCCCGCGCTGGGGTCCCGAGGGGCTGCTGGAGAGCCAGAGGCTGGCAGCGACTATG
TGAAGTTCTCCAAGGAGAAGTACATCCTGGACTCATCGCCAGAGAACTCCACAAGGAAT
TGGAGGAGGAGCTCAAACCTCAGCAGCACGGATCTCCGCGAGCCATGCCTGGTACCATGGCC
GCATCCCCCGAGAGGTCTCGGAGACCTTGGTACAACGCAACGGCGACTTCCTCATCCGGG
ACTCGCTCACCAGCCTGGGCGACTATGTGCTCACGTGCCGCTGGCGCAACCAGGCCTTGC
ACTTCAAGATCAACAAGGTGGTGGTGAAGGCAGGCGAGAGCTACACACACATCCAGTACC
TGTTTGAGCAGGAGAGCTTTGACCACGTGCCCGCCCTCGTGCGCTATCATGTGGGCAGCC
GCAAGGCTGTGTGAGCAGAGTGGTGGCATCATCTACTGCCCCGTGAACCGCACCTTCC
CACTGCGCTACCTCGAGGCCAGCTATGGCCTGGGACAGGGGAGTAGCAAGCCTGCTAGCC
CCGTCAGCCCCCTCAGGCCCCAAGGGCAGCCACATGAAGCGGCGCAGCGCTACCATGACCG
ATGGGCTCACTGCTGACAAGGTCAACCGCAGCGATGGCTGCCCCACCAGTACGTGCGTGC
CCCGCCCTCGGGACTCCATCCGCGAGCTGTGCCCTCAGCATGGACCAGATCCAGACCTGC
ACTCACCCTATGTCGCCCATCTCCGAGAGCCCTAGCTCCCTGCCTACAGCACTGTAACCC
GTGTCCATGCCGCCCCCTGCAGCCCCCTTCTGCCACAGCATTGCTGCTCCCTGTCGCCC
GCTGTTCCAGTGAGCCCCAGCTGTGTCCCGAAGTGCCCCAAAGACCCATGGGGAGTCAG
ACAAGGGCCCCCACACCAGCCCCCTCCACACCCCTTGGCAAGGCCTCCCCGTACCATCAC
TCAGCAGCTACAGTGACCCGACTCTGGCCACTACTGCCAGCTCCAGCCTCCCGTGCGTG
GCAGCCGAGAGTGGGCAGCGACTGAGACCTCCAGCCAGCAGGCCAGGAGCTATGGGGAGA
GGCTAAAGGAAGTGTGAGAAAATGGGGCCCCCTGAAGGGGACTGGGGCAAGACCTTCACAG
TCCCCATCGTGAAGTCACTTCTTCTTCAACCCGGCCACCTTCCAGTCACTACTGATCC
CCAGGGATAACCGGCCACTGGAGGTGGGCCTTCTGCGCAAGGTCAAGGAGCTGCTGGCAG
AAGTGGATGCCCGGACGCTGGCCCCGCATGTACCAAGGTGGACTGCCTGGTTGCTAGGA
TACTGGGCGTTACCAAGGAGATGCAGACCTAATGGGAGTCCGCTGGGGCATGGAAGTGC
TCACCTCCCCCATGGCCGGCAGCTACGCCTAGACCTGCTGGAAGGTTCCACACCATGT
CCATCATGCTGGCCGTGGACATCCTGGGCTGCACCGGCTCTGCGGAGGAGCGGGCAGCGC
TGCTGCACAAGACCATTAGCTGGCGCCGAGCTACGGGGGACTATGGGCAACATGTTCA
GCTTCGCGCGGTCATGGGTGCCCTGGACATGGCTCAGATTTCTCGGCTGGAGCAGACAT
GGGTGACCTTGGCGCAGCGACACACAGAGGGTGCCATCCTGTACGAGAAGAAGCTCAAGC
CTTTTCTCAAGAGCCTCAACGAGGGCAAAGAAGGCCCGCCGCTGAGCAACACCAGTTTC
CTCATGTGCTGCCCCCTCATACCTGCTGGAGTGTGACTCGGCCCCACCAGAGGGCCCTG
AGCCCTGGGGCAGCACGGAGCACGGCGTGGAGGTGGTGTGGCTCACCTGGAGGCCGCCC
GCACAGTGGCACACCACGGAGGCTGTACCACACCAATGCTGAAGTCAAGCTGCAGGGGT
TCCAGGCCCCGGCGGAGCTCCTGGAGGTGTTTACGACGGAGTTCCAGATGCGCCTTCTCT
GGGGCAGTCAGGGTGCCAGCAGCAGCCAGGCCCGGCGCTATGAGAAGTTCGACAAGGTCC
TCACTGCCCTGTCCACAAGCTGGAACCTGCTGTCCGCTCCAGCGAGCTGTA

FIGURE 14

```
><Tue May 2 15:06:10 PDT 2000 DNA61601 [min]
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA61601
><subunit 1 of 1, 703 aa, 1 stop
><MW: 77088, pI: 8.35, NX(S/T): 2
MTAVGRRCPALGSRGAAGEPEAGSDYVKFSKEYILDSSPEKLHKELEEBLKLSSTD LRS
HAWYHGRIPREVSETLVQRNGDFLIRDSLTS LGDYVLT CRWRNQALHFKINKVVVKAGES
YTHIQYLFEQESFDHVPALVRYHVGSRKAVSEQSGAIIYCPVNRTFPLRYLEASYGLGQG
SSKPASFPVSPSGPKGSHMKRRSVTMTDGLTADKVTRSDGCPTSTSLPRPRDSIRSCALSM
DQIPDLHSPMSPISESPSSPAYSTVTRVHAAPAAPSATALPASPVARCSSEPQLCPGSAP
KTHGESDKGPHTSPSHTLGKASPSPSLSSYSDPDSGHYCQLQPPVGRSREWAATETSSQQ
ARSYGERLKELENGAPEGDWGKTFTVPIVEVTSSFNPATFQSLLIPRDNRPLEVGLLRK
VKELLA EVDARTLARHVT KVDCLVARILGVTKEMQTLMGVRWGMELLTLPHGRQLRLDLL
ERFHTMSIMLAVDILGCTGSAEEERAA LLHKT IQLAELRGTMGNMFSFAAVMGALDMAQI
SRLEQTVVTLRQRHTEGAILYEKKLPFLKSLNEGKEGPPLSNTTTFPHVLP LITLLECDS
APPEGPEPWGSTEHGVEVVL AHLEAARTVAHHGGLYHTNAEVKLQGFQARPELLEV FSTE
FQMRLWGSQGASSSQARRYEKFDKVL TALSHKLEPAVRSEL
```

FIGURE 15

CAAACTTGCCTCGCGGAGAGCGCCAGCTTGACTTGAATGGAAGGAGCCCGAGCCCGCGGAGCGCAGCTGAGA
CTGGGGGAGCGCGTTTCGGCCTGTGGGGCGCCGCTCGGCGCCGGGGCGCAGCAGGGAAGGGGAAGCTGTGGTCTG
CCCTGCTCCACGAGGCGCCACTGGTGTGAACCGGGAGAGCCCTGGGTGGTCCCGTCCCCTATCCCTCCTTTAT
ATAGAAACCTTCCACACTGGGAAGGCAGCGGCAGGCAGGAGGGCTCATGGTGAGCAAGGAGGCCGGCTGATCT
GCAGGCGCACAGCATTCGAGTTTACAGATTTTACAGATACCAAATGGAAGGCGAGGAGGCAGAACAGCCTGC
CTGGTTCATCAGCCCTGGCGCCAGGCGCATCTGACTCGGCACCCCTGCAGGCACCATGGCCAGAGCCGGG
TGCTGCTGCTCCTGCTGCTGCTGCCGCCACAGCTGCACCTGGGACCTGTGCTTGCCGTGAGGGCCCCAGGATTT
GGCCGAAGTGCGGCCACAGCCTGAGCCCCGAAGAGAACGAATTTGCGGAGGAGGAGCCGGTGCTGGTACTGAG
CCCTGAGGAGCCCGGGCCTGGCCAGCCGCGGTGAGCTGCCCCGAGACTGTGCCTGTTCCAGGAGGGCGTCG
TGGACTGTGGCGGTATTGACCTGCGTGAGTTCCCGGGGACCTGCCTGAGCACACCAACCACCTATCTCTGCAG
AACAACCAGCTGGAAGATCTACCTGAGGAGCTCTCCCGGCTGCACCGGCTGGAGACACTGAACCTGCAAAA
CAACCGCCTGACTTCCCAGGGCTCCAGAGAAGGCGTTTGAGCATCTGACCAACCTCAATTACCTGTACTTGG
CCAATAACAAGCTGACCTTGGCACCCCGCTTCTGCCAAACGCCCTGATCAGTGTGGAATTTGCTGCCAACTAT
CTCACCAAGATCTATGGGCTCACCTTTGGCCAGAAGCCAACTTGAGGTCTGTGTACCTGCACAACAACAAGCT
GGCAGACGCCGGGCTGCCGGACAACATGTTCAACGGCTCCAGCAACGTCGAGGTCTCATCTGTCCAGCAACT
TCCTGCGCCACGTGCCAAGCACCTGCCGCTGCCCTGTACAAGCTGCACCTCAAGAACAAAGCTGGAGAAG
ATCCCCCGGGGGCCTTCAGCGAGCTGAGCAGCCTGCGCGAGCTATACCTGCAGAACAACTACCTGACTGACGA
GGCCTTGACAACGAGACCTTCTGGAAGCTCTCCAGCTGGAGTACCTGGATCTGTCCAGCAACAACCTGTCTC
GGGTCCAGCTGGGCTGCCGCGCAGCCTGGTGCTGTGCACTTGGAGAAGAACGCCATCCGGAGCGTGAGCGCG
AATGTGCTGACCCCCATCCGAGCCTGGAGTACCTGTCTGTGCACAGCAACCAGCTGCGGGAGCAGGGCATCCA
CCCACTGGCCTTCCAGGGCCTCAAGCGTTGCACACGGTGACCTGTACAACAACGCGCTGGAGCGCGTGCCCA
GTGGCCTGCCTCGCCGCTGCGCACCCCTCATGATCTGCACAACCAGATCACAGGCATTGGCCGCGAAGACTTT
GCCACCACCTACTTCTGGAGGAGCTCAACCTCAGTACAACCGCATCACAGCCACAGGTGCACCGCGACGC
CTTCCGCAAGCTGCGCCTGCTGCGCTCGCTGGACCTGTCCGGCAACCGGCTGCACACGCTGCCACCTGGGCTGC
CTCGAAATGTCCATGTGCTGAAGGTCAAGCGCAATGAGCTGGCTGCCTTGGCACGAGGGGGCGCTGGCGGGCATG
GCTCAGCTGCGTGAGCTGTACCTCACCAGCAACCGACTGCGCAGCCGAGCCCTGGGCCCCCGTGCCTGGGTGGA
CCTCGCCCATCTGCAGCTGCTGGACATCGCCGGGAATCAGCTCACAGAGATCCCCGAGGGGCTCCCCGAGTCAC
TTGAGTACCTGTACCTGCAGAACAAAGATTAGTGCGGTGCCCGCCAATGCCTTCGACTCCACGCCCCAACCTC
AAGGGGATCTTTCTCAGGTTTAAACAAGCTGGCTGTGGGCTCCGTGGTGACAGTGCCTTCCGGAGGCTGAAGCA
CCTGCAGGTCTTGGACATTGAAGGCAACTTAGAGTTTGGTGACATTTCCAAGGACCGTGGCCGCTTGGGGAAGG
AAAAGGAGGAGGAGGAAGAGGAGGAGGAGGAGGAGGAGGAAACAAGATAGTGACAAGGTGATGCAGATGTGACC
TAGGATGATGGACCGCCGACTCTTTTCTGCAGCACACGCCTGTGTGCTGTGAGCCCCCACTCTGCCGTGCTC
ACACAGACACACCCAGCTGCACACATGAGGCATCCACATGACACGGGCTGACACAGTCTCATATCCCCACCCC
TTCCACGGCGTGTCCACGGCCAGACACATGCACACATCACACCCTCAAACACCCAGCTCAGCCACACACA
ACTACCTTCAAACACCACAGTCTCTGTACACCCCCACTACCGCTGCCACGCCCTCTGAATCATGCAGGGAA
GGGTCTGCCCCCTGCCCTGGCACACACAGGCACCCATTCCCTCCCCCTGCTGACATGTGTATGCGTATGCATACA
CACCACACACACACATGCACAAGTCATGTGCGAACAGCCCTCCAAAGCCTATGCCACAGACAGCTCTTGCCC
CAGCCAGAATCAGCCATAGCAGCTCGCCGTCTGCCCTGTCCATCTGTCCGTCCGTTCCCTGGAGAAGACACAAG
GGTATCCATGCTCTGTGGCCAGGTGCCTGCCACCCTCTGGAACCTCACAAAAGCTGGCTTTTATTCCTTTCCCAT
CCTATGGGGACAGGAGCCTTCAGGACTGCTGGCCTGGCCTGGCCACCCTGCTCCTCCAGGTGCTGGGCAGTCA
CTCTGCTAAGAGTCCCTCCCTGCCACGCCCTGGCAGGACACAGGCACCTTTCCAATGGGCAAGCCAGTGAGG

FIGURE 15 Continued

CAGGATGGGAGAGCCCCCTGGGTGCTGCTGGGGCCTTGGGGCAGGAGTGAAGCAGAGGTGATGGGGCTGGGCTG
AGCCAGGGAGGAAGGACCCAGCTGCACCTAGGAGACACCTTTGTTCTTCAGGCCTGTGGGGGAAGTTCCGGGTG
CCTTTATTTTTTATTCTTTCTAAGGAAAAAATGATAAAAATCTCAAAGCTGATTTTCTTGTTATAGAAAAA
CTAATATAAAGCATTATCCCTATCCCTGCAAAAAA

FIGURE 16

MEGEEAEQPAWFHQPWRRPGASDSAPPAGTMAQSRVLLLLLLLLPPQLHLGPVLAVRAPGFGR
SGGHSLSPEENEFAEEEPVLVLSPEEPGPGPAAVSCPRDCACSQEGVVD CGGIDLREFPGD
LPEHTNHLSQLNNQLEKIYPEELSRHRLLETNLQNNRLTSRGLPEKA FEHLTNLNYLYLA
NNKLT LAPRFLPNALISVDFAANYLTKIYGLTFGQKPNLRSVYLHNNKLADAGLPDNMFNG
SSNVEVLILSSNFLRHVPKHLPPALYKLHLKNNKLEKIPPGAFSELSSLRELYLQNNYLT D
EGLDNETFWKLSSLEYLDLSSNNLSRV PAGLPRSLVLLHLEKNAIRSVDANVLTPIRSLEY
LLLHSNQLREQGIHPLAFQGLKRLHTVHLYNNALERVPSGLPRRVRTL MILHNQITGIGRE
DFATTYFLEELNLSYNRITSPQVHRDAFRKLRLRLSLDLSGNRLHTLPPGLPRNVHVLKVK
RNEIAALARGALAGMAQLRELYLTSNRLRSRALGPRAWVDLAHLQLLDIAGNQLTEIPEGL
PESLEYLYLQNNKISAVPANAFDSTPNLKGIFLRFNKLAVGSVVD SAFRRLKHLQVLDIEG
NLEFGDISKDRGLGKEKEEEEEEEEEEEETR

Signal sequence:

amino acids 1-48

N-glycosylation site.

amino acids 243-247, 310-314, 328-332, 439-443

Casein kinase II phosphorylation site.

amino acids 68-72, 84-88, 246-250, 292-296, 317-321, 591-595

N-myristoylation site.amino acids 19-25, 107-113, 213-219, 217-223, 236-242, 335-341,
477-483, 498-502, 539-545, 548-554**Leucine zipper pattern.**amino acids 116-138, 251-273, 258-280, 322-344, 464-486,
471-493, 535-557

FIGURE 17

AGTCCTGCCCAGCTCTTGGATCAGTCTGCTGGCCGAGGAGCCCGGTGGAGCCAGGGGTGACCCTGGAGCCCAGC
CTGCCCCGAGGAGGCCCCGGCTCAGAGCCATGCCAGGTGTCTGTGATAGGGCCCCCTGACTTCCTCTCCCCGTCT
GAAGACCAGGTGCTGAGGCCTGCCTTGGGCAGCTCAGTGGCTCTGAACTGCACGGCTTGGGTAGTCTCTGGGCC
CCACTGCTCCCTGCCTCAGTCCAGTGGCTGAAAGACGGGCTTCCATTGGGAATTGGGGGCCACTACAGCCTCC
ACGAGTACTCCTGGGTCAAGGCCAACCTGTCAAGAGGTGCTTGTGTCCAGTGTCTTGGGGGTCAACGTGACCAGC
ACTGAAGTCTATGGGGCCTTCACCTGCTCCATCCAGAACATCAGCTTCTCCTCCTTCACTCTTCAGAGAGCTGG
CCCTACAAGCCACGTGGCTGCGGTGCTGGCCTCCCTCCTGGTCTGCTGGCCCTGCTGCTGGCCGCCCTGCTCT
ATGTCAAGTGCCGTCTCAACGTGCTGCTCTGGTACCAGGACGCGTATGGGGAGGTGGAGATAAACGACGGGAAG
CTCTACGACGCCTACGTCTCCTACAGCGACTGCCCGAGGACCGCAAGTTCGTGAACCTTCATCTAAAGCCGCA
GCTGGAGCGGCGTCGGGGCTACAAGCTCTTCTGGACGACCGCGACCTCCTGCCGCGCGCTGAGCCCTCCGCCG
ACCTCTTGGTGAACCTGAGCCGCTGCCGACGCCTCATCGTGGTGCTTTCGGACGCCTTCTGAGCCGGGCCTGG
TGCAGCCACAGCTTCCGGGAGGGCCTGTGCCGGCTGCTGGAGCTCACCCGCAGACCCATCTTCATCACCTTCGA
GGGCCAGAGGCGCGACCCCGCGACCCGGCGCTCCGCCTGCTGCGCCAGCACCGCCACCTGGTGACCTTGCTGC
TCTGGAGGCCCCGGCTCCGTGACTCCTTCTCCGATTTTTGGAAAGAAGTGACGTGGCGCTGCCGCGGAAGGTG
CGGTACAGGCCCGGTGGAAGGAGACCCCGACGCGCTGCAGGACGACAAGGACCCCATGCTGATTCTTCGAGG
CCGAGTCCCTGAGGGCCGGGCCCTGGACTCAGAGGTGGACCCGGACCTGAGGGCGACCTGGGTATGCCCGCCC
AGCCCCACTCCCCAACTGGAGAAGCTCAGCACAGGGCGGAGTGGGGGCAGGCACAGGGCACAGGGCCTGGAGGG
GCTCTAGGTGTTGAGGACTCTTCCCGGCACCGGGAGCCCCCTGCACGGCCTCTGCCCTGGAGGTGCTCGGCCCTC
GGTCTGCCTGGGAACCTCCTGGGCCTCACAGGCCATCACAGCAGGGGGTGAGCAGGGGCAGCCCCCTGGCAGTGG
GTCTGGGCCAAGGCTGTGGGTGGCCACCTCAGGCGTCTCGGTCTCCCCACCCAGGTGTCCGGGGGCCTGTTTT
TGGAGAGCCATCAGCTCCACCGCACACCAGTGGGTCTCGCTGGGAGAGAGCCGGAGCAGCGAAGTGGACGTCT
CGGATCTCGGCTCGCGAACTACAGTGCCCGCACAGACTTCTACTGCCTGGTGTCCAAGGATGATATGTAGCTC
CCACCCAGAGTGCAGGATCA

FIGURE 18

MPGVCDRAPDFLSPSEDQVLRPALGSSVALNCTAWVVS GPHCSLPSVQWLKDGLPLGIGGHYSLHEYSWVKANL
SEVLVSSVLGVNVTSTEVYGAFTCSIQNI SFSSFTLQ RAGPTSHVA AVLASLLVLLALLLAALLYVKRLNVLL
WYQDAYGEVBINDGKLYDAYVSYSDCPEDRK FVNFILKPQLERRRGYKLFDDRDL LPRAEPSADLLVNL SRCR
RLIVVLSDAFLSRAWCSHSFREGLCRLLELTRRPIFIFITFEGQRDP AHPALRLLRQHRHLVTLLLRPGSVTPS
SDFWKEVQLALPRKVRYRPVEGDPQTQLQDDKDPMLILRGVPEGRALDSEVDPDFEGDLGMPAQPHSPTGEAQ
HRAEWGQAQGTGPGGALGVEDSSRHREPLHG LCPGGARPSVCLGTSWASQAITAGGEQQGPLAVGLGQCGWPP
QASRSPHPRCPGACFWRAISSTAHQWGLAGREPEQ RSGRLGSRLAKLQCPHRLLLPGVQG

Transmembrane domain:

Amino acids 120-140

N-glycosylation sites:

Amino acids 31-35;73-77;86-90;102-106;
217-221

N-myristoylation sites:

Amino acids 25-31;53-59;59-65;84-90;
94-100;376-382;380-386;384-390;388-394;
401-407;406-412;414-420;425-431;429-43
5;
435-441;437-443;485-491

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 430-441

Leucine zipper pattern:

Amino acids 123-145

FIGURE 19

GAAAGCTATAGGCTACCCATTTCAGCTCCCCTGTGAGAGACTCAAGCTTTGAGAAAGGCTAGCAAAGAGCAAGGA
AAGAGAGAAAACAACAAAGTGGCGAGGCCCTCAGAGTGAAAGCGTAAGGTTTCAGTCAGCCTGCTGCAGCTTTGC
AGACCTCAGCTGGGCATCTCCAGACTCCCCTGAAGGAAGAGCCTTCTCACCCAAACCCACAAAAGATGCTGAA
AAAGCCTCTCTCAGCTGTGACCTGGCTCTGCATTTTCATCGTGGCCTTTGTGAGCCACCCAGCGTGGCTGCAGA
AGCTCTCTAAGCACAAAGACACCAGCACAGCCACAGCTCAAAGCGGCCAACTGCTGTGAGGAGGTGAAGGAGCTC
AAGGCCCAAGTTGCCAACCTTAGCAGCCTGCTGAGTGAACGAAACAAGCAGGAGAGGGGACTGGGTGAGCGT
GGTCATGCAGGTGATGGAGCTGGAGAGCAACAGCAAGCGCATGGAGTCGCGGCTCACAGATGCTGAGAGCAAGT
ACTCCGAGATGAACAACCAAATTGACATCATGCAGCTGCAGGCAGCACAGACGGTCACTCAGACCTCCGCAGAT
GCCATCTACGACTGCTCTTCCCTCTACCAGAAGAACTACCGCATCTCTGGAGTGTATAAGCTTCTCTCTGATGA
CTTCTTGGGCAGCCCTGAACTGGAGGTGTTCTGTGACATGGAGACTTCAGGCGGAGGCTGGACCATCATCCAGA
GACGAAAAGTGGCCTTGTCTCTTCTACCGGACTGGAAGCAGTACAAGCAGGGCTTTGGCAGCATCCGTGGG
GACTTCTGGCTGGGGAACGAACACATCCACCGGCTCTCCAGACAGCCAACCCGGCTGCGTGTAGAGATGGAGGA
CTGGGAGGGCAACCTGCGCTACGCTGAGTATAGCCACTTTGTTTGGGCAATGAACTCAACAGCTATCGCCTCT
TCCTGGGGAACCTAGCTGGCAATGTGGGGAACACGCCCTCCAGTATCATAACAACACAGCCTTCAGCACCAAGG
ACAAGGACAATGACAACTGCTTGGACAAGTGTGCACAGCTCCGCAAAGGTGGCTACTGGTACAACCTGCTGCACA
GACTCCAACCTCAATGGAGTGTAATAACCGCTGGGTGAGCACAATAAGCACCTGGATGGCATCACCTGGTATGG
CTGGCATGGATCTACCTACTCCCTCAAACGGGTGGAGATGAAAATCCGCCCAGAAGACTTCAAGCCTTAAAAGG
AGGCTGCCGTGGAGCACGGATACAGAACTGAGACACGTGGAGACTGGATGAGGGCAGATGAGGACAGGAAGAG
AGTGTTAGAAAGGGTAGGACTGAGAAACAGCCTATAATCTCCAAAGAAAGAATAAGTCTCCAAGGAGCACAAAA
AAATCATATGTACCAAGGATGTTACAGTAAACAGGATGAACTATTTAAACCCACTGGGTCTGCCACATCCTTC
TCAAGGTGGTAGACTGAGTGGGGTCTCTCTGCCCAAGATCCCTGACATAGCAGTAGCTTGTCTTTCCACATGA
TTTGTCTGTGAAAGAAAATAATTTTGAGATCGTTTTATCTATTTTCTCTACGGCTTAGGCTATGTGAGGGCAAA
ACACAAATCCCTTTGCTAAAAAGAACCATATTATTTTGATTCTCAAAGGATAGGCCTTTGAGTGTAGAGAAAG
GAGTGAAGGAGGCAGGTGGGAAATGGTATTTCTATTTTAAATCCAGTGAAATTATCTTGAGTCTACACATTAT
TTTTAAACACAAAAATTTGTTCCGGCTGGAACCTGACCCAGGCTGGACTTGCAGGGGAGGAACTCCAGGGCACTGC
ATCTGGCGATCAGACTCTGAGCACTGCCCCTGCTCGCCTTGGTCATGTACAGCACTGAAAGGAATGAAGCACCA
GCAGGAGGTGGACAGAGTCTCTCATGGATGCCGGCACAAAACCTGCCTTAAATATTATAGTTAATACAGGTAT
ATCTATTTTTATTACTTTGTAAGAAACAAGCTCAAGGAGCTTCCTTTTAAATTTTGTCTGTAGGAAATGGTTG
AAAATGAAGGTAGATGGTGTATAGTTAATAATAAATGCTGTAAATAAGCATCTCACTTTGTAAAAATAAAT
ATTGTGGTTTTGTTTTAAACATTCAACGTTTCTTTCTCTACAATAAACACTTTCAAAATGTG

FIGURE 20

MLKKPLSAVTWLCIFIVAFVSHPAWLQKLSKHKTPAQPOLKAANCCEEVKELKAQVANLSSLLSELNKKQERDW
VSVVMQVMELESNSKRME SRLTDAESKYSEMNNQIDIMQLQAAQTVTQTSADAIYDCSSLYQKNYRISGVYKLP
PDDFLGSPLELVFCDMETSGGGWTIIQRRKSGLVSFYRDWKQYKQGFGSIRGDFWLGNEHIHRLSRQPTRLRVE
MEDWEGNLRVYAEYSHFVLGNELNSYRLFLGNYTGNVGNDALQYHNNTAFSTKDKDNDNCLDKCAQLRKGGYWYN
CCTDSNLNGVYYRLGEHNKHLDGITWYGWHGSTYSLKRVEMKIRPEDFKP

FIGURE 21

TGCGGCGACCGTCGTACACCATGGGCCTCCACCTCCGCCCCCTACCGTGTGGGGCTGCTCCCGGATGGCCTCCTG
TTCTCTTGCTGCTGCTAATGCTGCTCGCGGACCCAGCGCTCCCGGCCGGACGTACCCCCCAGTGGTGCTGGT
CCCTGGTGATTTGGGTAACCAACTGGAAGCCAAGCTGGACAAGCCGACAGTGGTGCACTACCTCTGCTCCAAGA
AGACCGAAAGCTACTTCACAATCTGGCTGAACCTGGAACCTGCTGCTGCCGTGCATCATTGACTGCTGGATTGAC
AATATCAGGCTGGTTTACAACAAAACATCCAGGGCCACCCAGTTTCTGATGGTGTTGGATGTACGTGTCCCTGG
CTTTGGGAAGACCTTCTCACTGGAGTTCTTGGACCCAGCAAAAGCAGCGTGGGTTCCTATTTCCACACCATGG
TGGAGAGCCTTGTGGGCTGGGGCTACACACGGGGTGAGGATGTCCGAGGGGCTCCCTATGACTGGCGCCGAGCC
CCAAATGAAACGGGGCCCTACTTCTGGCCCTCCGCGAGATGATCGAGGAGATGTACCAGCTGTATGGGGGGCC
CGTGGTGCTGGTTGCCACAGTATGGGCAACATGTACACGCTCTACTTTCTGCAGCGGCAGCCGAGGCCTGGA
AGGACAAGTATATCCGGGCCTTCGTGTCACTGGGTGCGCCCTGGGGGGGCGTGGCCAAGACCTGCGCGTCTCTG
GCTTCAGGAGACAACAACCGGATCCCAGTCATCGGGCCCCCTGAAGATCCGGGAGCAGCAGCGGTGCTGCTC
CACCAGCTGGCTGCTGCCCTACAACATACACATGGTCACCTGAGAAGGTGTTCTGTCAGACACCCACAATCAACT
ACACACTGCGGGACTACCGCAAGTTCTTCCAGGACATCGGCTTTGAAGATGGCTGGCTCATGCGGCAGGACACA
GAAGGGCTGGTGGAAGCCACGATGCCACCTGGCGTGAGCTGCACTGCCCTCTATGGTACTGGCGTCCCCACACC
AGACTCCTTCTACTATGAGAGCTTCCCTGACCGTGACCTTAAATCTGCTTTGGTGACGGCGATGGTACTGTGA
ACTTGAAGAGTGCCCTGCAGTGCCAGGCCTGGCAGAGCCGCCAGGAGCACCAGTGTGCTGCAGGAGCTGCCA
GGCAGCGAGCACATCGAGATGCTGGCCAACGCCACCCCTGGCCCTATCTGAAACGTGTGCTCCTTGGGCCCCTG
ACTCCTGTGCCACAGGACTCCTGTGGCTCGGCCGTGGACCTGCTGTTGGCCTCTGGGGCTGTCATGGCCCCACGC
GTTTTGCAAAGTTTGTGACTCACCATTCAAGGCCCGAGTCTTGGAAGTGTGAAGCATCTGCCATGGGGAAGTGC
TGTTTGTATCCTTCTCTGTGGCAGTGAAGAAGGAAGAAATGAGAGTCTAGACTCAAGGGACACTGGATGGCA
AGAATGCTGCTGATGGTGGAACCTGTGTGACCTTAGGACTGGCTCCACAGGGTGGACTGGCTGGGCCCCCTGGTCC
CAGTCCCTGCCTGGGGCCATGTGTCCCCCTATTCTGTGGGCTTTTCATACTTGCCCTACTGGGCCCCCTGGCCCCG
CAGCCTTCTATGAGGGATGTTACTGGGCTGTGGTCTGTATCCCAAGAGGTCCCAGGGATCGGCTCCTGGCCCCCT
CGGGTGACCCCTTCCACACACAGCCACAGATAGGCCTGCCACTGGTCATGGGTAGCTAGAGCTGCTGGCTTCC
CTGTGGCTTAGCTGGTGGCCAGCCTGACTGGCTTCTGGGCGAGCCTAGTAGCTCCTGCAGGCAGGGGCAGTTT
GTTGCGTTCTTCTGTGGTTCCAGGCCCTGGGACATCTCACTCCACTCCTACCTCCCTTACCACCAGGAGCATTC
AAGCTCTGGATTGGGCAGCAGATGTGCCCCCAGTCCCGCAGGCTGTGTTCCAGGGGCCCTGATTTCTCGGATG
TGCTATTGGCCCCAGGACTGAAGCTGCCTCCCTTCAACCTGGGACTGTGGTTCCAAGGATGAGAGCAGGGGTG
GAGCCATGGCCTTCTGGGAACCTATGGAGAAAGGAATCCAAGGAAGCAGCCAAGGCTGCTCGCAGCTTCCCTG
AGCTGCACCTCTTGCTAACCCACCATCACACTGCCACCTGCCCCAGGGTCTCACTAGTACCAAGTGGGTGAG
CACAGGGCTGAGGATGGGGCTCCTATCCACCCTGGCCAGCACCAGCTTAGTGCTGGGACTAGCCAGAACTT
GAATGGGACCTGAGAGAGCCAGGGTCCCCCTGAGGCCCCCTAGGGGCTTTCTGTCTGCCCCAGGGTGTCCA
TGGATCTCCCTGTGGCAGCAGGCATGGAGAGTCAGGGCTGCCTTCATGGCAGTAGGCTCTAAGTGGGTGACTGG
CCACAGGCCGAGAAAAGGGTACAGCCTCTAGGTGGGGTTCCTCAAAGACGCCTTCAGGCTGGACTGAGCTGCTCT
CCCACAGGGTTTCTGTGCAGCTGGATTTTCTCTGTGTCATACATGCCTGGCATCTGTCTCCCTTGTTCCTGAG
TGGCCCCACATGGGGCTCTGAGCAGGCTGTATCTGGATTCTGGCAATAAAAGTACTCTGGATGCTGTAAAAAA
AAAAAAAAAAAAAAAA

FIGURE 22

```
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA44189
><subunit 1 of 1, 412 aa, 1 stop
><MW: 46658, pI: 6.65, NX(S/T): 4
MGLHLRPYRVGLLPDGILLFLLLLLMLLADPALPAGRHPVVLVPGDLGNQLEAKLDKPTVVHYLCSKKTESYFT
IWLNLLELLLPVIIDCWIDNIRLVYNKTSRATQFPDGVDRVVPFGKTFSLFELDPSKSSVGSYFHTMVESLVGW
GYTRGEDVRGAPYDWRRAPNENGPYFLALREMIEMYQLYGGPVVLVAHSMGNMYTLYFLQRQPQAWKDKYIRA
FVSLGAPWGGVAKTLRLVSLASGDNNRIPVIGPLKIREQQRSVSTSWLLPYNYTWSPEKVFTPTINYTLRDYR
KFFQDIGFEDGWLMRQDTEGLVEATMPPGVQLHCLYGTGVPTPDSFYYESFPDRDPKICFGDGDGTVNLKSALQ
CQAWQSRQEHQVLLQELPGSEHIEMLANATTLAYLKRVLG
```

Important features:

Signal peptide:

amino acids 1-28

Potential lipid substrate binding site:

amino acids 147-164

N-glycosylation sites.

amino acids 99-102, 273-276, 289-292 and 398-401

Lipases, serine proteins

amino acids 189-201

Beta-transducin family Trp-Asp repeat

amino acids 353-365

FIGURE 23

GAGCCACCTACCCTGCTCCGAGGCCAGGCCTGCAGGGCCTCATCGGCCAGAGGGTGATCAGTGAGCAGAAGGAT
GCCCCGTGGCCGAGGCCCGCCAGGTGGCTGGCGGGCAGGGGGACGGAGGTGATGGCGAGGAAGCGGAGCCAGAGG
GGATGTTCAAGGCCTGTGAGGACTCCAAGAGAAAAGCCCGGGGCTACCTCCGCCTGGTGGCCCTGTTTGTGCTG
CTGGCCCTGCTCGTGCTGGCTTCGGCGGGGGTGCTACTCTGGTATTTCTAGGGTACAAGGCGGAGGTGATGGT
CAGCCAGGTGTACTCAGGCAGTCTGCGTGTACTCAATCGCCACTTCTCCCAGGATCTTACCCGCGGGGAATCTA
GTGCCTTCCGCAGTGAAACCGCCAAAGCCCAAGATGCTCAAGGAGCTCATCACCAGCACCCGCCTGGGAAGT
TACTACAACTCCAGCTCCGTCTATTCTTTGGGGAGGGACCCCTCACCTGCTTCTTCTGGTTCATTCTCCAAAT
CCCCGAGCACCGCCGGCTGATGCTGAGCCCCGAGGTGGTGCAGGCAGTGTGGTGGAGGAGCTGCTGTCCACAG
TCAACAGCTCGGCTGCCGTCCCCTACAGGGCCGAGTACGAAGTGGACCCCGAGGGCCTAGTGATCCTGGAAGCC
AGTGTGAAGACATAGCTGCATTGAATTCCACGCTGGGTGTACCGCTACAGCTACGTGGGCCAGGGCCAGGT
CCTCCGGCTGAAGGGGCTGACCACCTGGCCTCCAGCTGCCTGTGGCACCTGCAGGGCCCCAAGGACCTCATGC
TCAAACCTCCGGCTGGAGTGGACGCTGGCAGAGTGCCGGGACCGACTGGCCATGTATGACGTGGCCGGGCCCTG
GAGAAGAGGCTCATCACCTCGGTGTACGGCTGCAGCCGCCAGGAGCCCGTGGTGGAGGTTCTGGCGTCCGGGGC
CATCATGGCGGTCTGCTGGAAGAAGGGCCTGCACAGCTACTACGACCCCTTCGTGCTCTCCGTGCAGCCGGTGG
TCTTCCAGGCCTGTGAAGTGAACCTGACGCTGGACAACAGGCTCGACTCCCAGGGCGTCTCTCAGCACCCCGTAC
TTCCCCAGCTACTACTCGCCCCAAACCCACTGCTCCTGGCACCTCACGGTGCCTCTCTGGACTACGGCTTGGC
CCTCTGGTTTGATGCCTATGCACTGAGGAGGCAGAAGTATGATTTGCCGTGCACCCAGGGCCAGTGGACGATCC
AGAACAGGAGGCTGTGTGGCTTGCGCATCCTGCAGCCCTACGCCGAGAGGATCCCCGTGGTGGCCACGGCCGGG
ATCACCATCAACTTCACCTCCCAGATCTCCCTCACGGGGCCCGGTGTGCGGGTGCACTATGGCTTGTAACCA
GTCGGACCCCTGCCTGGAGAGTTCTCTGTTCTGTGAATGGACTCTGTGTCCCTGCCTGTGATGGGGTCAAGG
ACTGCCCCAACGGCCTGGATGAGAGAACTGCGTTTGCAGAGCCACATTCCAGTGCAAAGAGGACAGCACATGC
ATCTCACTGCCCCAAGGTCTGTGATGGGCAGCCTGATTGTCTCAACGGCAGCGATGAAGAGCAGTGCCAGGAAGG
GGTGCCATGTGGGACATTACCTTCCAGTGTGAGGACCGGAGCTGCGTGAAGAAGCCCAACCCGAGTGTGATG
GGCGGCCCGACTGCAGGGACGGCTCGGATGAGGAGCACTGTGACTGTGGCCTCCAGGGCCCTCCAGCCGCATT
GTTGGTGGAGCTGTGCTCCTCCGAGGGTGAGTGGCCATGGCAGGCCAGCCTCCAGGTTCCGGGTGACACATCTG
TGGGGGGGCCCTCATCGCTGACCGCTGGGTGATAACAGCTGCCCACTGCTTCCAGGAGGACAGCATGGCCTCCA
CGGTGCTGTGGACCGTGTTCCTGGGCAAGGTGTGGCAGAACTCGCGCTGGCCTGGAGAGGTGTCTTCAAGGTG
AGCCGCTGCTCCTGCACCCGTACCACGAAGAGGACAGCCATGACTACGACGTGGCGCTGCTGCAGCTCGACCA
CCCCGTGGTGGCTCGGCCGCCGTGCGCCCCGTCTGCTTGGCCGCGCTCCCACTTCTTCGAGCCCGGCCTGC
ACTGCTGGATTACGGGCTGGGGCGCCTTGCGCGAGGGCGGCCCATCAGCAACGCTCTGCAGAAAGTGGATGTG
CAGTTGATCCACAGGACCTGTGCAGCGAGGCCTATCGCTACCAGGTGACGCCACGCATGCTGTGTGCCGGCTA
CCGCAAGGGCAAGAAGGATGCCTGTGAGGGTGAAGTGGTCCGCTGGTGTGCAAGGCACTCAGTGGCCGCT
GGTTCCTGGCGGGGCTGGTCACTGGGGCCTGGGCTGTGGCCGGCCTAACTACTTCGGCGTCTACACCCGCATC
ACAGGTGTGATCAGCTGGATCCAGCAAGTGGTGACCTGAGGAACTGCCCCCTGCAAAGCAGGGGCCACCTCCT
GGACTCAGAGAGCCAGGGCAACTGCCAAGCAGGGGGACAAGTATTCTGGCGGGGGTGGGGGAGAGAGCAGGC
CCTGTGGTGGCAGGAGGTGGCATCTGTCTCGTCCCTGATGTCTGCTCCAGTGATGGCAGGAGGATGGAGAAGT
GCCAGCAGCTGGGGGTCAAGACGTCCCCTGAGGACCCAGGGCCACACCCAGCCCTTCTGCTCCCAATTCTCTC
TCCTCCGTCCCCCTCCTCCACTGCTGCCTAATGCAAGGCAGTGGCTCAGCAGCAAGAATGCTGGTTCTACATCC
CGAGGAGTGTCTGAGGTGCGCCCCACTCTGTACAGAGGCTGTTTGGGCAGCCTTGCTCCAGAGAGCAGATTCC
AGCTTCGGAAGCCCTGGTCTAACTTGGGATCTGGGAATGGAAGGTGCTCCCATCGGAGGGGACCCCTCAGAGCC
CTGGAGACTGCCAGGTGGGCCTGCTGCCACTGTAAGCCAAAAGGTGGGGAAGTCCCTGACTCCAGGGTCTTGGC
CCACCCCTGCCTGCCACCTGGGCCCTCACAGCCAGACCCCTCACTGGGAGGTGAGCTCAGCTGCCCTTTGGAAT

FIGURE 23 Continued

AAAGCTGCCTGATCAAAAAAAAAAAAAAAAAAAAAA

FIGURE 24

```
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA49152
><subunit 1 of 1, 802 aa, 1 stop
><MW: 88846, pI: 6.41, NX(S/T): 7
MPVAEAPQVAGGQGDGGDGEAEPEGMFKACEDSKRKARGYLRLVPLFVLLALLVLASAGVLLWYFLGYKAEVM
VSQVYSGSLRVLNRHFSQDLTRRESSAFRSETAKAQKMLKELITSTRLGTYNSSSVYSFGEGLTCFFWFILQ
IPEHRRMLMSPEVVQALLVEELLSTVNSSAAVPYRAEYEVDPGLVILEASVKDIAALNSTLGCYRYSYVGQGO
VLRLKGPDLHLASSCLWHLQGPDKLMLKRLLEWTLAECRDLAMYDVAGPLEKRLITSVYGCSRQEPVVEVLASG
AIMAVVWKKGLHSYYDPFVLSVQPVVFQACEVNLTLNRLDSQGVLSPTYFSPSYSPQTHCSWHLTVPSLDYGL
ALWFDAYALRRQKYDLPTQGGWTIQNRRLCGLRILQPYAERIPVVATAGITINFTSQISLTGPGVRVHYGLYN
QSDPCPGFEFLCSVNGLCVPACDGVKDCPNGLDERNCVCRATFQCKEDSTCISLPKVCDDGQPDCLNGSDDEQCQE
GVPCGTFTFQCEDRSCVKKPNPQCGRPDGCRDGSDEEHCDGGLQGPSSRIVGGAVSSEGEWPWQASLQVRGRHI
CGGALIADRWVITAACHCFQEDSMASITVLWTVFLGKQVWQNSRWPGEVSFKVSRLLLHPYHEEDSHDYDVALQLD
HPVVRSAAVRPVCLPARSHFFEPGLHCWITGWGALREGGPISNALQKVDVQLIPQDLCSEAYRYQVTPRMLCAG
YRKGGKDACQGDGGPLVCKALSGRWFLAGLVSWGLGCGRPNYFGVYTRITGVISWIIQQVVT
```

Important features:**Type II transmembrane domain:**

amino acids 46-67

Serine proteases, trypsin family, histidine active site.

amino acids 604-609

N-glycosylation sites.

amino acids 127-130, 175-178, 207-210, 329-332, 424-427, 444-447 and 509-512

Kringle domains.

amino acids 746-758 and 592-609

Homologous region to Kallikrein Light Chain:

amino acids 568-779

Homologous region to Low-density lipoprotein receptor:

amino acids 451-567

FIGURE 25

GCAACCTCAGCTTCTAGTATCCAGACTCCAGCGCCGCCCCGGGCGCGGACCCCAACCCGACCCAGAGCTTCTC
CAGCGGCGGCGCAGCGAGCAGGGCTCCCCGCCTTAACCTTCCTCCGCGGGGCCAGCCACCTTCGGGAGTCCGGG
TTGCCACCTGCAAACTCTCCGCCTTCTGCACCTGCCACCCCTGAGCCAGCGGGGGCCCCGAGCGAGTCATGG
CCAACGCGGGGGTGCAGCTGTGGGCTTCATTCTCGCCTTCCTGGGATGGATCGGCGCCATCGTCAGCACTGCC
CTGCCCCAGTGGAGGATTTACTCCTATGCCGGCGACAACATCGTGACCGCCAGGCCATGTACGAGGGGCTGTG
GATGTCTCGTGTGTCGAGAGCACCGGGCAGATCCAGTGCAAAGTCTTTGACTCCTTGCTGAATCTGAGCAGCA
CATTGCAAGCAACCCGTGCC'TTGATGGTGGTTGGCATCCTCCTGGGAGTGATAGCAATCTTTGTGGCCACCGTT
GGCATGAAGTGTATGAAGTGCTTGGAAGACGATGAGGTGCAGAAGATGAGGATGGCTGTCAATTGGGGGTGCGAT
ATTTCTTCTTGCAAGTCTGGCTATTTTAGTTGCCACAGCATGGTATGGCAATAGAATCGTTCAAGAATTCTATG
ACCCATGACCCCCAGTCAATGCCAGGTACGAATTTGGTCAGGCTCTCTTCACTGGCTGGGCTGCTGCTTCTCTC
TGCTTCTGGGAGGTGCCCTACTTTGCTGTTCTGTCCCGAAAAACAACCTCTTACCCAACACCAAGGCCCTA
TCCAAAACCTGCACCTTCCAGCGGGAAAGACTACGTGTGACACAGAGGCAAAAGGAGAAAAATCATGTTGAAACA
AACCGAAAATGGACATTGAGATACTATCATTAACATTAGGACCTTAGAATTTTGGGTATTGTAATCTGAAGTAT
GGTATTACAAAACAAACAAACAAACAAAAACCCATGTGTTAAATACTCAGTGCTAAACATGGCTTAATCTTA
TTTTATCTTCTTCTCAATATAGGAGGGAAGATTTTCCATTGTATTACTGCTTCCCATGAGTAATCATAC
TCAATGGGGGAAGGGGTGCTCCTTAAATATATATAGATATGTATATATACATGTTTTTCTATTAAAAATAGAC
AGTAAAATACTATTCTCATTATGTTGATACTAGCATACTTAAAATATCTCTAAAATAGGTAAATGTATTTAATT
CCATATTGATGAAGATGTTTATTGGTATATTTCTTTTTCGTCCTTATATACATATGTAACAGTCAAATATCAT
TTACTCTTCTTCATTAGCTTTGGGTGCCTTTGCCACAAGACCTAGCCTAATTTACCAAGGATGAATTTCTTCAA
TTCTTCATGCGTGCCCTTTTCATATACTTATTTTATTTTACCATAATCTTATAGCACTTGCATCGTTATTAA
GCCCTTATTTGTTTGTGTTTCATTGGTCTCTATCTCTGAATCTAACACATTTTCATAGCCTACATTTTAGTTT
CTAAAGCCAAGAAGAATTTATTACAAATCAGAACTTTGGAGGCAAATCTTCTGCATGACCAAAAGTGATAAATT
CCTGTTGACCTTCCACACAATCCCTGTACTCTGACCCATAGCACTCTTGTTTGCTTTGAAAATATTTGTCCAA
TTGAGTAGCTGCATGCTGTTCCCCCAGGTGTTGTAACACAACCTTTATTGATTGAATTTTAAAGCTACTTATTCA
TAGTTTATATCCCCCTAAACTACCTTTTTTGTTCCCCATTCCTTAATTGTATTGTTTTCCCAAGTGAATTATC
ATGCGTTTTATATCTTCTAATAAGGTGTGGTCTGTTTGTCTGAACAAAGTGCTAGACTTCTGGAGTGATAAT
CTGGTGACAAATATTCTCTCTGTAGCTGTAAGCAAGTCACTTAATCTTCTACCTCTTTTTTCTATCTGCCAAA
TTGAGATAATGATACTTAACCAGTTAGAAGAGGTAGTGTGAATATTAATTAGTTTATATTACTCTTATTCTTTG
AACATGAACATATGCCTATGTAGTGTCTTTATTTGCTCAGCTGGCTGAGACACTGAAGAAGTCACTGAACAAAAC
CTACACACGTACCTTCATGTGATTCACTGCCTTCCTCTCTCTACCAGTCTATTTCCACTGAACAAAACCTACAC
ACATACCTTCATGTGGTTTCAGTGCCTTCCTCTCTCTACCAGTCTATTTCCACTGAACAAAACCTACGCACATAC
CTTCATGTGGCTCAGTGCCTTCCTCTCTCTACCAGTCTATTTCCATTCTTTCAGCTGTGTCTGACATGTTGTG
CTCTGTTCCATTTTAAACAACCTGCTCTTACTTTTCCAGTCTGTACAGAATGCTATTTCACTTGAGCAAGATGATG
TAATGGAAAGGGTGTGGCACTGGTGTCTGGAGACCTGGATTTGAGTCTTGGTGCTATCAATCACCGTCTGTGT
TTGAGCAAGGCATTTGGCTGCTGTAAGCTTATGCTTCATCTGTAAGCGGTGGTTTGTAAATTCCTGATCTTCCC
ACCTCACAGTGTGTTGTGGGGATCCAGTGAGATAGAATACATGTAAGTGTGGTTTTGTAAATTTAAAAAGTGCT
ATACTAAGGGAAAGAATTGAGGAATTAACGCATACGTTTGGTGTGCTTTTCAAATGTTTGAAAATAAAAAA
AATGTTAAG

FIGURE 26

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA52185
><subunit 1 of 1, 211 aa, 1 stop
><MW: 22744, pI: 8.51, NX(S/T): 1
MANAGLQLLGFI LAFLGWIGAIVSTALPQWRIYSYAGDNIVTAQAMYEGLWMSCVSTGQ
IQCKVFDSLNLSS TLQATRALMVVGILLGVIAIFVATVGMKCMKCLEDDEVQKMRMAVIG
GAIFLLAGLAILVATAWYGNRIVQEFYDPMTPVNNARYEFGQALFTGWAAASLCLLGALLC
CSCPRKTTSYPTPRPYPKPAPSSGKDYV

Important features:**Signal peptide:**

amino acids 1-21

Transmembrane domains:

amino acids 82-102, 118-142 and 161-187

N-glycosylation site.

amino acids 72-75

PMP-22 / EMP / MP20 family proteins

amino acids 70-111

ABC-2 type transport system integral membrane protein

amino acids 119-133

FIGURE 27

GGCTCGAGCGTTTCTGAGCCAGGGGTGACCATGACCTGCTGCGAAGGATGGACATCCTGCA
ATGGATTCAGCCTGCTGGTTCTACTGCTGTTAGGAGTAGTTCTCAATGCGATACCTCTAAT
TGTCAGCTTAGTTGAGGAAGACCAATTTTCTCAAACCCCATCTCTTGCTTTGAGTGGTGG
TTCCCAGGAATTATAGGAGCAGGTCTGATGGCCATTCCAGCAACAACAATGTCCTTGACAG
CAAGAAAAAGAGCGTGCTGCAACAACAGAACTGGAATGTTTCTTTCATCATTTTTTCAGTGT
GATCACAGTCATTGGTGCTCTGTATTGCATGCTGATATCCATCCAGGCTCTCTTAAAAGGT
CCTCTCATGTGTAATTCTCCAAGCAACAGTAATGCCAATTGTGAATTTTCATTGAAAAACA
TCAGTGACATTCATCCAGAATCCTTCAACTTGCACTGGTGGTTTTTCAATGACTCTTGTGCACC
TCCTACTGGTTTCAATAAACCCACCAGTAACGACACCATGGCGAGTGGCTGGAGAGCATCT
AGTTTCCACTTCGATTCTGAAGAAAACAAACATAGGCTTATCCACTTCTCAGTATTTTTAG
GTCTATTGCTTGTTGGAATTCTGGAGGTCCTGTTTGGGCTCAGTCAGATAGTCATCGGTTT
CCTTGGCTGTCTGTGTGGAGTCTCTAAGCGAAGAAGTCAAATTGTGTAGTTTAATGGGAAT
AAAATGTAAGTATCAGTAGTTTGAAAAAAAAAAAA

FIGURE 28

MTCCEGWTSCNGFSLLVLLLLGVVLNAIPLIVSLVEEDQFSQNPISCFEWWFPGIIGAGLM
AIPATTMSLTARKRACCNNRTGMFLSSFFSVITVIGALYCMLISIQALLKGPLMCNSPSNS
NANCEFSLKNISDIHPESFNLQWFFNDSCAPPTGFNKPTSNDTMASGWRASSFHFDSEENK
HRLIHFSVFLGLLLVGILEVLFGLSQIVIGFLGCLCGVSKRRSQIV

FIGURE 29

GGCACGAGGCGGCGGGGCAGTCGCGGGATGCGCCCCGGGAGCCACAGCCTGAGGCCCTCAGG
TCTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTGCCACTTC
CAGCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAAGCA
TGGAGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGTTTGC
AGCCTTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGGCCGCGAGACCTGCTGCAGCGCTAT
GATTCTAAGCCCATTTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCTCTGAGT
TAGAACTGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGAATGAAGA
CTGGATCGAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGATTTGTCAC
ACTCTGACAGAGAAGCTTGTGGCCATGACAATGGGCTCTGGGGCCAAGATGAAGACTTCAG
CCAGTGTCAGCGACATCATTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGGATGATGTTGT
GAAGTCGATGTACCCCTCCGTTGGACCCCCAACTCCTGGACGCACGGACGACTGCCCTGCTC
CTGTCTGTCAGTCACCTGGTGCTGGTGACAAGGAATGCCTGCCATCTGACGGGAGGCCTGG
ACTGGATTGACCAGTCTCTGTGCGCTGCTGAGGAGCATTTGGAAGTCCTTCGAGAAGCAGC
CCTAGCTTCTGAGCCAGATAAAGGCCTCCAGGCCCTGAAGGCTTCCTGCAGGAGCAGTCT
GCAATTTAGTGCCTACAGGCCAGCAGCTAGCCATGAAGGCCCTGCGGCCATCCCTGGATG
GCTCAGCTTAGCCTTCTACTTTTTCTATAGAGTTAGTTGTTCTCCACGGCTGGAGAGTTC
AGCTGTGTGTGCATAGTAAAGCAGGAGATCCCCGTGAGTTTATGCCTCTTTTGCAGTTGCA
AACTGTGGCTGGTGAGTGGCAGTCTAATACTACAGTTAGGGGAGATGCCATTCACTCTCTG
CAAGAGGAGTATTGAAAACCTGGTGGACTGTCAGCTTTATTTAGCTCACCTAGTGTTTTCAA
GAAAATTGAGCCACCGTCTAAGAAATCAAGAGGTTTCACATTAAATTAGAATTTCTGGCC
TCTCTCGATCGGTCAGAATGTGTGGCAATTCTGATCTGCATTTTCAGAAGAGGACAATCAA
TTGAAACTAAGTAGGGGTTTCTTCTTTTGGCAAGACTTGTA CTCTCTCACCTGGCCTGTTT
CATTTATTTGTATTATCTGCCTGGTCCCTGAGGCGTCTGGGTCTCTCCTCTCCCTTGCAAG
TTTGGGTTTGAAGCTGAGGAACTACAAAGTTGATGATTTCTTTTTTATCTTTATGCCTGCA
ATTTTACCTAGCTACCACTAGGTGGATAGTAAATTTATACTTATGTTTCCCTCAAAAAAA
AAAAAA

FIGURE 30

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPSE
LELDDVVITNPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMKTS
ASVSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLSVSHLVLVTRNACHLTGGL
DWIDQSLSAEEHLEVLREAALASEPDKGLPGPEGFLQEQSAI

FIGURE 31

CTGTCGTCTTTGCTTCAGCCGAGTCGCCACTGGCTGCCTGAGGTGCTCTTACAGCCTGTT
CCAAGTGTGGCTTAATCCGTCTCCACCACCAGATCTTTCTCCGTGGATTCTCTGCTAAGA
CCGCTGCCATGCCAGTGACGGTAACCCGCACCACCATCACAAACCACCAGACGTCATCTTC
GGGCTGGGGTCCCCCATGATCGTGGGGTCCCCCTCGGGCCCTGACACAGCCCCTGGGTCTC
CTTCGCCTGCTGCAGCTGGTGTCTACCTGCGTGGCCTTCTCGCTGGTGGCTAGCGTGGGCG
CCTGGACGGGGTCCATGGGCAACTGGTCCATGTTACCTGGTGTCTTGCTTCTCCGTGAC
CCTGATCATCCTCATCGTGGAGCTGTGCGGGCTCCAGGCCCGCTTCCCCCTGTCTTGGCGC
AACTTCCCCATCACCTTCGCCTGCTATGCGGCCCTCTTCTGCCTCTCGGCCTCCATCATCT
ACCCACCACCTATGTCCAGTTCCTGTCCCACGGCCGTTTCGCGGGACCACGCCATCGCCGC
CACCTTCTTCTCCTGCATCGCGTGTGTGGCTTACGCCACCGAAGTGGCCTGGACCCGGGCC
CGGCCCCGGCGAGATCACTGGCTATATGGCCACCGTACCCGGGCTGCTGAAGGTGCTGGAGA
CCTTCGTTGCCTGCATCATCTTCGCGTTCATCAGCGACCCCAACCTGTACCAGCACCCAGCC
GGCCCTGGAGTGGTGCCTGGCGGTGTACGCCATCTGCTTCATCCTAGCGGCCATCGCCATC
CTGCTGAACCTGGGGGAGTGCACCAACGTGCTACCCATCCCCTTCCCCAGCTTCTGTTCGG
GGCTGGCCTTGCTGTCTGTCTCTCTATGCCACCGCCCTTGTTCTCTGGCCCCCTCTACCA
GTTTCGATGAGAAGTATGGCGGCCAGCCTCGGCGCTCGAGAGATGTAAGCTGCAGCCGCAGC
CATGCCTACTACGTGTGTGCCTGGGACCGCCGACTGGCTGTGGCCATCCTGACGGCCATCA
ACCTACTGGCGTATGTGGCTGACCTGGTGCCTCTGCCCACCTGGTTTTTGTCAAGGTCTA
AGACTCTCCCAAGAGGCTCCCGTTCCCTCTCCAACCTCTTTGTTCTTCTTGCCGAGTTTTT
CTTTATGGAGTACTTCTTTCCCTCCGCCTTTCTCTGTTTTCTCTTCTTCTCCCTCCC
TCCCACCTTTTTCTTTCCCTTCCCAATTCCTTGCACTCTAACCAGTTCTTGGATGCATCTTC
TTCCTTCCCTTTCTTCTGCTGTTTTCTTCCCTGTGTTGTTTTGTTGCCACATCCTGTTTT
CACCCCTGAGCTGTTTCTCTTTTTCTTTCTTTCTTTTTTTTTTTTTTTTTTAAGACGGAT
TCTCACTCTGTGGCCAGGCTGGAGTGCAGTGGTGCATCTCAGCTCACTGCAACCCCCGC
CTCCTGGGTTCAAGCGATTCTCCTCCCCAGCCTCCCAAGTAGCTGGGAGGACAGGTGTGA
GCTGCCGCACCCAGCCTGTTTCTTTTTTCCACTCTTCTTTTTTCTCATCTCTTTTCTGGG
TTGCCTGTGGCTTTCTTATCTGCCTGTTTTGCAAGCACCTTCTCCTGTGTCTTGGGAGC
CCTGAGACTTCTTTCTCTCCTTGCTCCACCCACCTCCAAAGGTGCTGAGCTCACATCCAC
ACCCCTTGACGCCGTCCATGCCACAGCCCCCAAGGGGCCCCATTGCCAAAGCATGCCTGC
CCACCCTCGCTGTGCCTTAGTCAGTGTGTACGTGTGTGTGTGTGTGTGTGTTGGGGGGTGGG
GGGTGGGTAGCTGGGGATTGGGCCCTCTTTCTCCAGTGGAGGAAGGTGTGCAGTGTACTT
CCCCTTTAAATTAAAAACATATATATATATATATTTGGAGGTCAGTAATTTCCAATGGGC
GGGAGGCATTAAGCACCGACCCTGGGTCCCTAGGCCCGCCTGGCACTCAGCCTTGCCAGA
GATTGGCTCCAGAATTTTTGCCAGGCTTACAGAACACCCACTGCCTAGAGGCCATCTTAAA
GGAAGCAGGGGCTGGATGCCTTTCATCCCAACTATTCTCTGTGGTATGAAAAAG

FIGURE 32

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA58727

<subunit 1 of 1, 322 aa, 1 stop

<MW: 35274, pI: 8.57, NX(S/T): 1

MPVTVTRTTITTTTTSSSGLGSPMIVGSPRALTQPLGLLRLLQLVSTCVAFSLVASVGAWT
GSMGNWSMFTWCFCFSVTLLIILIVELCGLQARFPLSWRNFPITFACYAALFCLSASIIYPT
TYVQFLSHGRSRDHAIAATFFSCIACVAYATEVAWTRARPGEITGYMATVPGLLKVLETfV
ACIIFAFISDPNLYQHQPALWCVAVYAICFILAAIAILLNLGECTNVLPPIPFPSFLSGLA
LLSVLLYATALVLWPLYQFDEKYGGQPRRSRDVSCSRSHAYYVCAWDRRLAVAILTAINLL
AYVADLVHSAHLVFVKV

Important features:**Transmembrane domains:**

amino acids 41-60 (type II), 66-85, 101-120, 137-153, 171-192,
205-226, 235-255 and 294-312

N-glycosylation site.

amino acids 66-69

Glycosaminoglycan attachment site.

amino acids 18-21

FIGURE 33

GCCAGGTGTGCAGGCCGCTCCAAGCCCAGCCTGCCCCGCTGCCGCCACCATGACGCTCCTCCCCGGCCTCCTGT
TTCTGACCTGGCTGCACACATGCCTGGCCCACCATGACCCCTCCCTCAGGGGGCACCCCCACAGTCACGGTACC
CCACACTGCTACTCGGCTGAGGAACTGCCCCTCGGCCAGGCCCCCCCCACACCTGCTGGCTCGAGGTGCCAAGTG
GGGGCAGGCTTTGCCTGTAGCCCTGGTGTCCAGCCTGGAGGCAGCAAGCCACAGGGGGAGGCACGAGAGGCCCT
CAGCTACGACCCAGTGCCCGGTGCTGCCGCCGGAGGAGGTGTTGGAGGCAGACACCCACCAGCGCTCCATCTCA
CCCTGGAGATAACCGTGTGGACACGGATGAGGACCGCTATCCACAGAAGCTGGCCTTCGCCGAGTGCCCTGTGCAG
AGGCTGTATCGATGCACGGACGGGCCGCGAGACAGCTGCCGCTCAACTCCGTGCCGCTGCTCCAGAGCCTGCTGG
TGCTGCCGCCGCCGCCCTGCTCCCGCGACGGCTCGGGGCTCCCCACACCTGGGGCCTTTGCCTTCCACACCGAG
TTCATCCACGTCCCCGTCGGCTGCACCTGCGTGCTGCCCCGTTCAGTGACCGCCGAGGCCGTGGGGCCCCCTA
GACTGGACACGTGTGCTCCCCAGAGGGCACCCCCTATTTATGTGTATTTATTGTTATTTATATGCCTCCCCAA
CACTACCCTTGGGGTCTGGGCATTCCCCGTGTCTGGAGGACAGCCCCCACTGTTCTCCTCATCTCCAGCCTCA
GTAGTTGGGGGTAGAAGGAGCTCAGCACCTCTTCCAGCCCTTAAAGCTGCAGAAAAGGTGTACACGGCTGCCT
GTACCTTGGCTCCCTGTCTGCTCCCGGCTTCCCTTACCCTATCACTGGCCTCAGGCCCCGCAGGCTGCCTCTT
CCCAACCTCCTTGGAAGTACCCCTGTTTCTTAACAATTATTTAAGTGACGTGTATTATTAACTGATGAACA
CATCCCCAAA

FIGURE 34

MTLLPGLLFLTWLHTCLAHHDPSLRGHPHSHGTPHCYSAEELPLGQAPPHELLARGAKWGQALPVALVSSLEAAS
HRGRHERPSATTQCPVLRPEEVLEADTHQRSISPWRYRVDTDEDRYPQKLAFAECLCRGCIDARTGRETAALNS
VRLQSLVLVLRRRPCSRDGSGGLPTPGAFAFHTEFIHVPVGCTCVLPRSV

Signal peptide:	Amino acids 1-18
Tyrosine kinase phosphorylation site:	Amino acids 112-121
N-myristoylation sites:	Amino acids 32-38;55-61;133-139
Leucine zipper pattern:	Amino acids 3-25
Homologous region to IL-17:	Amino acids 99-195

FIGURE 35

GTGGCTTCATTTTCAGTGGCTGACTTCCAGAGAGCAATATGGCTGGTTCCCCAACATGCCTC
ACCCATCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGC
TGGTCGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTCCAAAGTAAAGCAAGTTGA
CTCTATTGTCTGGACCTTCAACACAACCCCTCTTGTCAACATACAGCCAGAAGGGGGCACT
ATCATAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCC
TGAAGCTCAGCAAATGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTC
ATCACTCCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAG
CCTAAAGTCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACAT
GCTGCATGGAACATGGGGAAGAGGATGTGATTTATACCTGGAAGGCCCTGGGGCAAGCAGC
CAATGAGTCCCATAATGGGTCCATCCTCCCCATCTCCTGGAGATGGGGAGAAAGTGATATG
ACCTTCATCTGCGTTGCCAGGAACCCCTGTGAGCAGAACTTCTCAAGCCCCATCCTTGCCA
GGAAGCTCTGTGAAGGTGCTGCTGATGACCCAGATTCTCCATGGTCCTCCTGTGTCTCCT
GTTGGTGCCCCCTCTGCTCAGTCTCTTTGTACTGGGGCTATTTCTTTGGTTTCTGAAGAGA
GAGAGACAAGAAGAGTACATTGAAGAGAAGAAGAGAGTGGACATTTGTCTGGGAAACTCCTA
ACATATGCCCCCATTTCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAATAGAAC
AATCCTAAAGGAAGATCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAAAGATG
GAAAATCCCCACTCACTGCTCACGATGCCAGACACACCAAGGCTATTTGCCTATGAGAATG
TTATCTAGACAGCAGTGCCTCCCCTAAGTCTCTGCTCA

FIGURE 36

MAGSPTCLTLIYILWQLTGSAASGPVKELVGSVGGAVTFPLKSKVKQVDSIVWTFNTTPLV
TIQPEGGTIIIVTQNRNRERVDFFPDGGYSLKLSKLKKNDSGIYYVGIYSSSLQQPSTQEYVL
HVEHLSKPKVTMGLQSNKNGTCVTNLTCCEHGEEDVIYTWKALGQAANESHNGSILPIS
WRWGESDMTFICVARNPVSRNFSSPILARKLCEGAADDPDSSMVLLCLLLVPLLLSLFVLG
LFLWFLKRERQEEYIEKKRVDICRETPNICPHSGENTYDTPHTNRTILKEDPANTVYS
TVEIPKKMENPHSLLTMPDTPRLFAYENVI

FIGURE 37

GTTCCTCATAGTTGGCGTCTTCTAAAGGAAAACTAAAAATGAGGAACTCAGCGGACCGGGAGCGACGCAGCT
TGAGGGAAGCATCCCTAGCTGTTGGCGCAGAGGGGCGAGGCTGAAGCCGAGTGGCCCGAGGTGTCTGAGGGGCT
GGGGCAAAGGTGAAAGAGTTTCAGAACAAAGCTTCCTGGAACCCATGACCCATGAAGTCTTGTGACATTTATAC
CGTCTGAGGGTAGCAGCTCGAACTAGAAGAAGTGGAGTGTGCGCAGGGACGGCAGTATCTCTTTGTGTGACCC
TGGCGGCCTATGGGACGTGGCTTCAGACCTTTGTGATACACCATGCTGCGTGGGACGATGACGGCGTGGAGAG
GAATGAGGCCTGAGGTCACACTGGCTTGCCTCCTCTAGCCACAGCAGGCTGCTTTGCTGACTTGAACGAGGTC
CCTCAGGTACCCGTCCAGCCTGCGTCCACCGTCCAGAAGCCCGGAGGCACTGTGATCTTGGGCTGCGTGGTGA
ACCTCCAAGGATGAATGTAACCTGGCGCCTGAATGGAAGGAGCTGAATGGCTCGGATGATGCTCTGGGTGTCC
TCATCACCCACGGGACCCTCGTCATCACTGCCCTTAACAACCACACTGTGGGACGGTACCAGTGTGTGGCCCGG
ATGCCTGCGGGGGCTGTGGCCAGCGTGCCAGCCACTGTGACACTAGCCAATCTCCAGGACTTCAAGTTAGATGT
GCAGCACGTGATTGAAGTGGATGAGGGAACACAGCAGTCAATTGCCTGCCACCTGCCTGAGAGCCACCCCAAAG
CCCAGGTCCGGTACAGCGTCAAACAAGAGTGGCTGGAGGCTCCAGAGGTAACCTGATCATGCCCTCAGGG
AACCTCCAGATTGTGAATGCCAGCCAGGAGGACGAGGGCATGTACAAGTGTGCAGCCTACAACCCAGTGACCCA
GGAAGTGAAACCTCCGGCTCCAGCGACAGGCTACGTGTGCGCCGCTCCACCGCTGAGGCTGCCCCGCATCATCT
ACCCCCCAGAGGCCCAAACCATCATCGTCACCAAAGGCCAGACTCTCATTTCTGGAGTGTGTGGCCAGTGGAAATC
CCACCCCCACGGGTCACTGGGCCAAGGATGGGTCCAGTGTACCCGGCTACAACAAGACGCGCTTCTCTGTGAG
CAACCTCCTCATCGACACCACAGCGAGGAGGACTCAGGCACCTACCGCTGCATGGCCGACAATGGGGTTGGGC
AGCCCCGGGGCAGCGGTCACTCTACAATGTCCAGGTGTTTGAACCCCTGAGGTACCATGGAGCTATCCCAG
CTGGTCACTCCCCTGGGGCCAGAGTGCCAAGCTTACCTGTGAGGTGCGTGGGAACCCCCCGCTCCGTGTGTG
GCTGAGGAATGCTGTGCCCCCTCATCTCCAGCCAGCGCTCCGGCTCTCCCGCAGGGCCCTGCGCGTGTCTAGCA
TGGGGCTGAGGACGAAGGCGTCTACCAGTGCATGGCCGAGAACGAGGTGGGAGCGCCCATGCCGTAGTCCAG
CTGCGGACCTCCAGGCCAAGCATAACCCCAAGGCTATGGCAGGATGCTGAGCTGGCTACTGGCACACCTCCTGT
ATCACCTCCAACTCGGCAACCCTGAGCAGATGCTGAGGGGGCAACCGCGCTCCCCAGACCCCCAACGTCTAG
TGGGGCTGCTTCCCCGAAGTGTCCAGGAGAGAAGGGGCAGGGGGCTCCCGCCGAGGCTCCCATCATCTCTCAGC
TCGCCCCGCACCTCCAAGACAGACTCATATGAACTGGTGTGGCGGCCCTCGGCATGAGGGCAGTGGCCGGGCGCC
AATCCTCTACTATGTGGTGAAACACCGCAAGCAGGTCAAAATTCCTCTGACGATTGGACCATCTCTGGCATTC
CAGCCAAACAGCACCGCTGACCCTCACCAGACTTGACCCGGGAGCTTGTATGAAGTGGAGATGGCAGCTTAC
AACTGTGCGGGAGAGGGCCAGACAGCCATGGTCACTTCCGAACTGGACGGCGGCCCAAACCCGAGATCATGGC
CAGCAAAGAGCAGCAGATCCAGAGAGACGACCCTGGAGCCAGTCCCAGAGCAGCAGCCAGCCAGACCACGGCC
GCCTCTCCCCCCCCAGAAGCTCCCGACAGGCCCCACCATCTCCACGGCCTCCGAGACCTCAGTGTACGTGACCTGG
ATTCCCCGTGGGAATGGTGGGTTCCTAATCCAGTCTTCCGTGTGGAGTACAAGAAGCTAAAGAAAGTGGGAGA
CTGGATTCTGGCCACCAGCGCATCCCCCATCGCGGTGTCCGTGGAGATCACGGGCTAGAGAAAGGCACCT
CCTACAAGTTTTGAGTCCGGGCTCTGAACATGCTGGGGGAGAGCGAGCCAGCGCCCCCTCTCGGCCCTACGTG
GTGTCGGGCTACAGCGGTGCGTGTACGAGAGGCCCGTGGCAGGTCTTATATCACCTTCACGGATGCGGTCAA
TGAGACCACCATCATGCTCAAGTGGATGTACATCCAGCAAGTAACAACAACACCCCAATCCATGGCTTTTATA
TCTATTATCGACCCACAGACAGTGAATGATAGTACTACAAGAAGGATATGGTGAAGGGGACAAGTACTGG
CACTCCATCAGCCACCTGCAGCCAGAGACCTCCTACGACATTAAGATGCAGTGTCTCAATGAAGGAGGGGAGAG
CGAGTTCAGCAACGTGATGATCTGTGAGACCAAAGCTCGGAAGTCTTCTGGCCAGCCTGGTTCGACTGCCACCCC
CAACTCTGGCCCCACCAAGCGCCCTTCTGAAACCATAGAGCGGCGGTTGGGCACTGGGGCCATGGTGGCT
CGCTCCAGCGACCTGCCCTATCTGATTGTGCGGGTCTGCTGGGCTCCATCGTTCTCATCATCGTCACCTTCAT
CCCCCTCTGCTTGTGGAGGGCTGGTCTAAGCAAAAACATACAACAGACCTGGGTTTTCTCGAAGTGCCCTTC
CACCTCCTGCCGTATACTATGTTGCCATTGGGAGGACTCCCAGGCCACCAGGCCAGTGGACAGCCCTACCTC
AGTGGCATCAGTGGACGGGCTGTGCTAATGGGATCCACATGAATAGGGGCTGCCCCCTCGGCTGCAGTGGGCTA

FIGURE 37 Continued

CCCGGGCATGAAGCCCCAGCAGCACTGCCCAGGCGAGCTTCAGCAGCAGAGTGACACCAGCAGCCTGCTGAGGC
AGACCCATCTTGGCAATGGATATGACCCCCAAAGTCACCAGATCACGAGGGGTCCCAAGTCTAGCCCGGACGAG
GGCTCTTTCTTATACACACTGCCCCGACGACTCCACTCACCAGCTGCTGCAGCCCCATCACGACTGCTGCCAAGC
CCAGGAGCAGCCTGCTGCTGTGGGCCAGTCAGGGGTGAGGAGAGCCCCGACAGTCCTGTCTGGAAGCAGTGT
GGGACCTCCATTTCACTCAGGGCCCCCATGCTGCTTGGGCCCTTGTGCCAGTTGAAGAGGTGGACAGTCCTGAC
TCCTGCCAAGTGAGTGGAGGAGACTGGTGTCCCCAGCACCCCGTAGGGGCCCTACGTAGGACAGGAACCTGGAAT
GCAGCTCTCCCGGGGCCACTGGTGCGTGTGTCTTTTGAACACCCACCTCTCACAATTTAGGCAGAAGCTGATA
TCCCAGAAAGACTATATATTGTTTTTTTTTAAAAAAAAGAAGAAAAAGAGACAGAGAAAATTGGTATTTA
TTTTTCATTTATAGCCATATTTATATATTTATGCACTTGTAATAAATGTATATGTTTTATAATTCTGGAGAGA
CATAAGGAGTCCTACCCGTTGAGGTTGGAGAGGGAAAAATAAGAAGCTGCCACCTAACAGGAGTCACCCAGGAA
AGCACCGCACAGGCTGGCGCGGGACAGACTCCTAACCTGGGGCCTCTGCAGTGGCAGGCGAGGCTGCAGGAGGC
CCACAGATAAGCTGGCAAGAGGAAGGATCCCAGGCACATGGTTCATCACGAGCATGAGGGAACAGCAAGGGGCA
CGGTATCACAGCCTGGAGACACCCACACAGATGGCTGGATCCGGTGCTACGGGAAACATTTTCTTAAGATGCCC
ATGAGAACAGACCAAGATGTGTACAGCACTATGAGCATTAAAAAACCTTCCAGAATCAATAATCCGTGGCAACA
TATCTCTGTAAAAACAAACACTGTAACTTCTAAATAAATGTTTAGTCTTCCCTGTAAAA

FIGURE 38

MLRGMTAWRGMREVTTLACLLLATAGCFADLNEVPQVTVQPASTVQKPGGTVILGCVVEPPRMNVTWRLNGKE
LNGSDDALGVLITHGTLVITALNNHTVGRYQCVARMPAGAVASVPATVTLANLQDFKLDVQHVEVDEGNTAVI
ACHLPESHKPAQVRYSVKQEWLEASRGNYLIMPSGNLQIVNASQEDEGMYKCAAYNPVTQEVKTSGSSDRLRVR
RSTAEAAARIITYPPEAQTIIIVTKGQSLILECVASGIPPPRVTWAKDGSSVTGYNKTRFLLSNLLIDTTSEEDSGT
YRCMADNGVGQPGAIVILYNVQVFEPPEVTMELSOLVIPWGQSAKLTCEVRGNPPPSVLWLRNAVPLISSQRLR
LSRRALRVLSMGPEDEGVYQCMANEVGSAAHVQLRTSRPSITPRLWQDAELATGTPPVSPSKLGNPEQMLRG
QPALPRPPTSVGPASPKCPGEGQGAPAEAPIILSSPRTSKTDSYELVWRPRHEGSGRAPILYYVVKHRKQVTN
SSDDWTISGIPANQHRLTLTRLDPGSLYEVEAAYNCAGEGQTAMVTFRTGRRPKPEIMASKEQQIQRDDPGAS
PQSSSQPDHGRSLSPPEAPDRPTISTASETSVYVTWIPRNGGFPFIQSFRVEYKKLKKVGDWILATSAIPPSRLS
VEITGLEKGTSYKFRVRALNMLGESEPSAPSRPYVVS GYSGRVYERPVAGPYITFTDAVNETTIMLKWMIYPAS
NNNTPIHGFYIYRPTDSDNDSYKDMVEGDKYWHISHLQPETS YDIKMQCFNEGGESEFSNVMICETKARK
SSGQPGRLPPPTLAPPQPPLPETIERPVGTGAMVARSSDLPYLIVGVVLGSIVLIIVTFIPFCLWRAWSKQKHT
TDLGFPRSALPPSCP YTMVPLGGLPGHQASGQPYLSGISGRACANGIHMNRGCPSAAVGYPGMKPQQHC PGELQ
QQSDTSSLLRQTHLGNGYDPQSHQITRGPKSSPDEGSFLYTL PDDSTHQLLQPHHDCCQRQE QPAAVGQSGVRR
APDSPVLEAVWDPPFHSGPPCCLGLVPVEEVDS PDSCQVSGGDWCPQHFPVGAYVGQEPGMQLSPGPLVRVSFET
PPLTI

Signal peptide:

amino acids 1-30

Transmembrane domain:

amino acids 16-30 (type II), 854-879

FIGURE 39

CATTTCCAACAAGAGCACTGGCCAAGTCAGCTTCTTCTGAGAGAGTCTCTAGAAGACATGA
TGCTACACTCAGCTTTGGGTCTCTGCCTCTTACTCGTCAAGTTTCTTCCAACCTTGCCAT
TGCAATAAAAAAGGAAAAGAGGCCTCCTCAGACACTCTCAAGAGGATGGGGAGATGACATC
ACTTGGGTACAACTTATGAAGAAGGTCTCTTTTATGCTCAAAAAAGTAAGAAGCCATTAA
TGGTTATTCATCACCTGGAGGATTGTCAATACTCTCAAGCACTAAAGAAAGTATTTGCCCA
AAATGAAGAAATACAAGAAATGGCTCAGAATAAGTTCATCATGCTAAACCTTATGCATGAA
ACCACTGATAAGAATTTATCACCTGATGGGCAATATGTGCCTAGAATCATGTTTGTAGACC
CTTCTTTAACAGTTAGAGCTGACATAGCTGGAAGATACTCTAACAGATTGTACACATATGA
GCCTCGGGATTTACCCCTATTGATAGAAAACATGAAGAAAGCATTAAAGACTTATTCAGTCA
GAGCTATAAGAGATGATGGAAAAAGCCTTCACTTCAAAGAAGTCAAATTTTCATGAAGAAA
ACCTCTGGCACATTGACAAATACTAAATGTGCAAGTATATAGATTTTGTAAATATTACTATT
TAGTTTTTTTAAATGTGTTTGCAATAGTCTTATTAAAATAAATGTTTTTTAAATCTGA

FIGURE 40

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA64896

<subunit 1 of 1, 166 aa, 1 stop

<MW: 19171, pI: 8.26, NX(S/T): 1

MMLHSALGLCLLLVTVSSNLAIKKEKRPPQTL SRGWGDDITWVQTYEEGLFYAQSKKP
LMVIHHLEDCQYSQALKKVFAQNEEIQEMAQNKFIMLNLMHETTDKNLSPDGQYVPRIMFV
DPSLTVRADIAGRYSNRLYTYEPRDLPLLIENMKKALRLIQSEL

Important features:

Signal peptide:

amino acids 1-23

N-myristoylation site.

amino acids 51-57

[illegible]

FIGURE 42

MDSLRLKMLISVAMLGAGAGVGYALLVIVTPGERRKQEMLKEMPLQDPRSREEAARTQQLLL
ATLQEAATTQENVAWRKNWMVGGEGGASGRSP

Signal peptide:

amino acids 1-18

[illegible]

FIGURE 43 Continued

TGGAGCGCCTCTCTCCTGAGCCTCAGTTTCCCTTTCCGTCTAATGAAGAACATGCCGTCTCGGTGTCTCAGGGC
TATTAGGACTTGCCCTCAGGAAGTGGCCTTGGACGAGCGTCATGTTATTTTCACAACTGTCCTGCGACGTTGGC
CTGGGACAGTCATGGAATGGCCCATGTCCCTCTGCTGCGTGGACGTCGCGGTGGGAGTGCCGAGCCAGAGGCG
GGGCCAGACGTGCGCCTGGGGGTGAGGGGAGGCGCCCCGGGAGGGCCTCACAGGAAGTTGGGCTCCCGCACCAC
CAGGCAGGGCGGGCTCCCGCCGCCCGCCGCCACCACCGTCCAGGGGCCGGTAGACAAAGTGGAAAGTCGCGCT
TGGGCTCGCTGCGCAGCAGGTAGCCCTTGATGCAGTGCGGCAGCGCGTCGTCCGCCAGCTGGAAGCAGCGCCCG
TCCACCAGCACGAACAGCCGGTGCGCCT

FIGURE 44

MCFLNKLLLLLAVLGWLFQIPTVPEDLFFLEEGPSYAFEVDTVAPHEGLDNAPVVDQQLLYTCCPYIGELRKLLA
SWVSGSSGRSGGFMRKITPTTTTSLGAQPSQTSQGLQAQLAQAFFHNQPPSLRRTVEFVAERIGSNCKHIKAT
LVADLVRQAESLLQEQLVTQGEEGDPAQLLEILCSQLCPHGAQALALGREFCQRKSPGAVRALLPEETPAAVL
SSAENIAVGLATEKACAWLSANITALIRREVKAASRTLRAQGPEPAARGERRGCSRA

Signal peptide:

amino acids 1-18

N-glycosylation site.

amino acids 244-248

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 89-93

Casein kinase II phosphorylation site.

amino acids 21-25, 167-171, 223-227

N-myristoylation site.

amino acids 100-106; 172-178, 207-213

Microbodies C-terminal targeting signal.

amino acids 278-282

[illegible]

FIGURE 46

MDFLLGLCLYWLLRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEAPHNLSGLLGLSLRY
NSLSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTLSSNQITQLPNTTFRPMPNLRSDLSYNK
LQALAPDLFHGLRKLTTLHMRANAIQFVPVRIFQDCRSKFLDIGYNQLKSLARNSFAGLFKLTLEHLEHNDLV
KVNFAHFPRLISLHSLCLRRNKVAIVVSSLDWVWNLEKMDLSGNEIEYMEPHVFETVPHLQSLQLDSNRLTYIE
PRIILNSWKSLSITLAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDVYAFHLCEDGAET
SGHLLSAVTNRSDLGPPASSATTLADGGEGQHDGTFEPATVALPGGEHAENAVQIHKVVTGTMALIFSEFLIVVL
VLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQMAAMSAQEYYVDYKPNHIEGALVIINEYGSCCTCHQQPAR
ECEV

FIGURE 47

AGCGGGTCTCGCTTGGGTTCCGCTAATTTCTGTCTGAGGCGTGAGACTGAGTTCATAGGGTCTTGGGTCCTCCCG
AACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGCGACCCAAGTGAGGGGCCCCGTGTTGGGGTCCTC
CCTCCCTTTGCATTCCCAACCCCTCCGGGCTTTGCGTCTTCTCTGGGACCCCCCTCGCCGGGAGATGGCCCGGTTG
ATGCGGAGCAAGGATTCGTCTGTCTGCTCTCTACTGGCCGCGGTGCTGATGGTGGAGAGCTCACAGATCGG
CAGTTCGCGGGCCAACTCAACTCCATCAAGTCTCTCTGGGCGGGGAGACGCTGGTCAGGCCGCCAATCGAT
CTGCGGGCATGTACCAAGGACTGGCATTCCGGCGGCAGTAAGAAGGGCAAAAACCTGGGGCAGGCCCTACCCTTGT
AGCAGTGATAAGGAGTGTGAAGTTGGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCTTCATGGTGTG
TCGGAGAAAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGCTGCAATAATGGCATCTGTA
TCCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGGATGGTACTCGGCACAGAGATCGAAACCAC
GGTCATTACTCAAACCATGACTTGGGATGGCAGAATCTAGGAAGACCACACACTAAGATGTCACATATAAAAGG
GCATGAAGGAGACCCCTGCCTACGATCATCAGACTGAGTTCGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCA
AAATCTGCAAAACCAAGTGTCTCCATCAGGGGGAAGTCTGTACCAACAACGCAAGAAGGGTTCTCATGGGCTGGAA
ATTTTCCAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAGTATGGAAGATGCCACCTACTCCTCCAAAGC
CAGACTCCATGTGTGTGAGAAAATTTGATCACCATTGAGGAACATCATCAATTCAGACTGTGAAGTTGTGTAT
TTAATGCATTATAGCATGGTGGAAAATAAGGTTGAGATGCAGAAGAATGGCTAAAAATAAGAAACGTGATAAGAA
TATAGATGATCACAAAAGGGAGAAAAGAAAACATGAAGTGAATAGATTAGAATGGGTGACAAATGCAGTGCAGC
CAGTGTTTCCATTATGCAACTTGTCTATGTAAATAATGTACACATTTGTGGAAAATGCTATTATTAAGAGAAC
AGCACACAGTGGAAATTAAGTATGAGTAGCATGTGACTTTCCAGAGTTTAGGTTGTGCTGGAGGAGAGGTTTC
CTTCAGATTGCTGATTGCTTATACAAATAACCTACATGCCAGATTTCTATTCAACGTTAGAGTTTAAACAAAATA
CTCCTAGAATAACTTGTATACAAATAGGTTCTAAAAATAAAATGCTAAACAAGAAATGAAAACATGGAGCATT
GTTAATTTACAACAGAAAATTACCTTTTGATTTGTAAACACTACTTCTGCTGTTCAATCAAGAGTCTTGGTAGAT
AAGAAAAAATCAGTCAATATTTCCAAATAATGCAAAATAATGGCCAGTGTGTTAGGAAGGCCTTTAGGAAGA
CAAATAAATAACAAACAAACAGCCACAATACTTTTTTTTCAAATTTTAGTTTACCTGTAATTAATAAGAAC
TGATACAAGACAAAACAGTTCCTTCAGATTCTACGGAATGACAGTATATCTCTCTTTATCCTATGTGATTCCCT
GCTCTGAATGCATTATATTTTCCAACTATACCCATAAATTTGTGACTAGTAAAATACTTACACAGAGCAGAATT
TTCACAGATGGCAAAAAAATTTAAAGATGTCCAATATATGTGGGAAAAGAGCTAACAGAGAGATCATTATTTCT
TAAAGATTGGCCATAACCTATATTTTGATAGAATTAGATTGGTAAATACATGTATTCATACATACTCTGTGGTA
ATAGAGACTTAAGCTGGATCTGTACTGCACTGGAGTAAGCAAGAAAATTTGGGAAAACCTTTTTCGTTTGTTCAGG
TTTTGGCAACACATAGATCATATGTCTGAGGCACAAGTTGGCTGTTTCATCTTTGAAACCAGGGGATGCACAGTC
TAAATGAATATCTGCATGGGATTTGCTATCATAATTTACTATGCAGATGAATTCAGTGTGAGGTCCTGTGTC
CGTACTATCCTCAAATTATTTATTTTATAGTGTGAGATCCTCAAATAATCTCAATTTTCAGGAGGTTTCACAAA
ATGTACTCCTGAAGTAGACAGAGTAGTGAGGTTTCATTGCCCTCTATAAGCTTCTGACTAGCCAATGGCATCAT
CCAATTTTCTTCCAAACCTCTGCAGCATCTGCTTTATTGCCAAAGGGCTAGTTTCGGTTTTCTGCAGCCATTG
CGGTTAAAAAATAAAGTAGGATAACTTGTAAAACCTGCATATTGCTAATCTATAGACACCACAGTTTCTAAAT
TCTTTGAAACCACTTTACTACTTTTTTTTAAACTTAACTCAGTTCTAAATACTTTGTCTGGAGCACAAAACAATA
AAAGGTTATCTTATAGTCGTGACTTTAAACTTTTGTAGACCACAATTCACCTTTTAGTTTTCTTTACTTAAAT
CCCATCTGCAGTCTCAAATTTAAGTTCTCCAGTAGAGATTGAGTTTGAGCCTGTATATCTATTAAAAATTTCA
ACTTCCACATATATTTACTAAGATGATTAAGACTTACATTTTCTGCACAGGTCTGCAAAAACAAAATTATAA
ACTAGTCCATCCAAGAACCAAGTTTGTATAAACAGGTTGCTATAAGCTTGTGAAATGAAATGGAACATTTCA
ATCAAACATTTCTATATAACAATTATTATTTTACAATTTGGTTTCTGCAATATTTTCTTATGTCCACCCTT
TTAAAAATATTATTTGAAGTAATTTATTTACAGGAAATGTTAATGAGATGTATTTTCTTATAGAGATATTTCT
TACAGAAAGCTTTGTAGCAGAATATATTTGCAGCTATTGACTTTGTAATTTAGGAAAAATGATAATAAGATAA
AATCTATTAAATTTTTCTCCTCTAAAACTGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAA

FIGURE 48

MAALMRSKDSSCCLLLLAAVLMVLESSQIGSSRAKLNSIKSSLGGETPGQAANRSAGMYQGLAFGGSKKGKNLGQ
AYPCSSDKECEVGRYCHSPHQSSACMVCRRKKRCHRDGMCCPSTRCNNGICIPVTESILTPHIPALDGTTRHR
DRNHGHYSNHDLGWQNLGRPHTKMSHIKGHEGDPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGS
HGLEIFQRCDCAKGLSCKVWKDATYSSKARLHVCQKI

Signal peptide:
amino acids 1-25

FIGURE 49

CGTGGGCCGGGGTTCGCGCAGCGGGCTGTGGGCGCGCCCGGAGGAGCGACCGCCGAGTTCT
CGAGCTCCAGCTGCATTCCCTCCGCGTCCGCCCCACGCTTCTCCCGCTCCGGGCCCCGCAA
TGGCCCAGGCAGTGTGGTTCGCGCCTCGGCCGCATCCTCTGGCTTGCCTGCCTCCTGCCCTG
GGCCCCGGCAGGGGTGGCCGCAGGCCTGTATGAACTCAATCTCACCACCGATAGCCCTGCC
ACCACGGGAGCGGTGGTGACCATCTCGGCCAGCCTGGTGGCCAAGGACAACGGCAGCCTGG
CCCTGCCCCGCTGACGCCACCTCTACCGCTTCCACTGGATCCACACCCCGCTGGTGCTTAC
TGGCAAGATGGAGAAGGGTCTCAGCTCCACCATCCGTGTGGTTCGGCCACGTGCCCCGGGAA
TTCCCGGTCTCTGTCTGGGTCACTGCCGCTGACTGCTGGATGTGCCAGCCTGTGGCCAGGG
GCTTTGTGGTCCTCCCCATCACAGAGTTCCTCGTGGGGACCTTGTTGTACCCAGAACAC
TTCCCTACCCTGGCCCAGCTCCTATCTCACTAAGACCGTCTGAAAGTCTCCTTCCTCCTC
CACGACCCGAGCAACTTCCTCAAGACCGCCTTGTTTCTCTACAGCTGGGACTTCGGGGACG
GGACCCAGATGGTGAAGACTCCGTGGTCTATTATAACTATTCCATCATCGGGACCTT
CACCGTGAAGCTCAAAGTGGTGGCGGAGTGGGAAGAGGTGGAGCCGGATGCCACGAGGGCT
GTGAAGCAGAAGACCGGGGACTTCTCCGCCTCGCTGAAGCTGCAGGAAACCTTCGAGGGCA
TCTAAGTGTGGGGCCCCACCTAATTACAGCCTTCCAAAAGATGACCGTGACCTTGAAGT
CCTGGGGAGCCCTCCTCTGACTGTGTGCTGGCGTCTCAAGCCTGAGTGCCCTCCGCTGGAG
GAAGGGGAGTGCCACCCTGTGTCCGTGGCCAGCACAGCGTACAACCTGACCCACACCTTCA
GGGACCCTGGGGACTACTGCTTCAGCATCCGGGCCGAGAATATCATCAGCAAGACACATCA
GTACCACAAGATCCAGGTGTGGCCCTCCAGAATCCAGCCGGCTGTCTTTGCTTTCCCATG
GCTACACTTATCACTGTGATGTTGGCCTTCATCATGTACATGACCCTGCGGAATGCCACTC
AGCAAAAGGACATGGTGGAGAACCCGGAGCCACCCTCTGGGGTCAAGTGCTGTGCCAGAT
GTGCTGTGGGCCTTTCTTGCTGGAGACTCCATCTGAGTACCTGGAAATTGTTCTGTAGAAC
CACGGGCTGCTCCCGCCCCTCTATAAGTCTGTCAAACTTACACCGTGTGAGCACTCCCCC
TCCCCACCCATCTCAGTGTTAACTGACTGCTGACTTGGAGTTTCCAGCAGGGTGGTGTGC
ACCACTGACCAGGAGGGGTTCAATTGCGTGGGGCTGTGGCCTGGATCATCCATCCATCTG
TACAGTTCAGCCACTGCCACAAGCCCCCTCCCTCTCTGTACCCCTGACCCAGCCATTAC
CCATCTGTACAGTCCAGCCACTGACATAAGCCCCACTCGGTACCACCCCTTGACCCCT
ACCTTTGAAGAGGCTTCGTGCAGGACTTTGATGCTTGGGGTGTTCGGTGTGACTCCTAGG
TGGGCCTGGCTGCCCCTGCCCCATTCTCTCATATTGGCACATCTGCTGTCCATTGGGGGT
TCTCAGTTTCTCCCCCAGACAGCCCTACCTGTGCCAGAGAGCTAGAAAAGAGGTCAATAA
GGGTAAAAATCCATAACTAAAGGTTGTACACATAGATGGGCACACTCACAGAGAGAAGTG
TGCATGTACACACACCACACACACACACACACACACAGAAATATAAACACATGCG
TCACATGGGCATTTAGATGATCAGCTCTGTATCTGGTTAAGTCGGTTGCTGGGATGCACC
CTGCACTAGAGCTGAAAGGAAATTTGACCTCCAAGCAGCCCTGACAGGTTCTGGGCCCCGG
CCCTCCCTTTGTGCTTTGTCTCTGCAGTTCTTGCGCCCTTTATAAGGCCATCCTAGTCCCT
GCTGGCTGGCAGGGGCTGGATGGGGGGCAGGACTAATACTGAGTGATTGCAGAGTGCTTT
ATAAATATCACCTTATTTTATCGAAACCCATCTGTGAACTTTCACTGAGGAAAAGGCCTT
GCAGCGGTAGAAGAGGTTGAGTCAAGGCCGGCGCGGTGGCTCACGCCTGTAATCCCAGCA
CTTTGGGAGGCCGAGGCGGTGGATCACGAGATCAGGAGATCGAGACCACCTGGCTAACA
CGGTGAAACCCGCTCTACTAAAAAATACAAAAAGTTAGCCGGGCGTGGTGGTGGGTGC
CTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATGGTGCGAACCCGGGAGGCGGAG
CTTGCACTGAGCCAGATGGCGCCACTGCACTCCAGCCTGAGTGACAGAGCGAGACTCTGT
CTCCA

FIGURE 50

MAQAVWSRLGRILWLACLLPWAPAGVAAGLYELNLTTDSPATTGAVVTISASLVAKDNGSL
ALPADAHLRYRFHWIHTPLVLTGKMEKGLSSTIRVVGHVPGEFPVSVWVTAADCWMCQPVAR
GFVVLPITEFLVGDLVVTQNTSLPWPSSYLTKTVLKVSFLLHDPSNFLKTALFLYSWDFGD
GTQMVTEDSVYYNYNSIIGTFTVKLVVAEWEVEPDATRAVKQKTGDFSASLKLQETLRG
IQVLGPTLIQTFQKMTVTLNFLGSPPLTVCWRLKPECLPLEEGECHPVSVASTAYNLTHTF
RDPGDYCFSSIRAENIISKTHQYHKIQVWPSRIQPAVFAPPCATLITVMLAFIMYMTLRNAT
QQKDMVENPEPPSGVRCCCQMC CGPFLLETPSEYLEIVRENHGLLPPLYKSVKTYTV

Important features of the protein:

Signal peptide:

amino acids 1-24

Transmembrane domain:

amino acids 339-362

N-glycosylation sites.

amino acids 34-37, 58-61, 142-145, 197-200, 300-303 and 364-367

FIGURE 51

CTATGAAGAAGCTTCCTGGAAAACAATAAGCAAAGGAAAACAAATGTGTCCCATCTCACAT
GGTTCTACCCCTACTAAAGACAGGAAGATCATAAACTGACAGATACTGAAATTGTAAGAGTT
GGAAACTACATTTTGCAAAGTCATTGAACTCTGAGCTCAGTTGCAGTACTCGGGAAGCCAT
GCAGGATGAAGATGGATACATCACCTTAAATATTAAAACTCGGAAACCAGCTCTCGTCTCC
GTTGGCCCTGCATCCTCCTCCTGGTGGCGTGTGATGGCTTTGATTCTGCTGATCCTGTGCG
TGGGGATGGTTGTCTGGGCTGGTGGCTCTGGGGATTTGGTCTGTGATGCAGCGCAATTACCT
ACAAGATGAGAATGAAAATCGCACAGGAACCTGCAACAATTAGCAAAGCGCTTCTGTCAA
TATGTGGTAAAACAATCAGAACTAAAGGGCACTTTCAAAGGTCATAAATGCAGCCCCGTGTG
ACACAACTGGAGATATTATGGAGATAGCTGCTATGGGTTCTTCAGGCACAACTTAACATG
GGAAGAGAGTAAGCAGTACTGCACTGACATGAATGCTACTCTCCTGAAGATTGACAACCGG
AACATTGTGGAGTACATCAAAGCCAGGACTCATTTAATTCGTTGGGTCGGATTATCTCGCC
AGAAGTCGAATGAGGTCTGGAAGTGGGAGGATGGCTCGGTTATCTCAGAAAATATGTTTGA
GTTTTTGGAAGATGAAAAGGAAATATGAATTGTGCTTATTTTCATAATGGGAAAATGCAC
CCTACCTTCTGTGAGAACAAACATTATTTAATGTGTGAGAGGAAGGCTGGCATGACCAAGG
TGGACCAACTACCTTAATGCAAAGAGGTGGACAGGATAACACAGATAAGGGCTTTATTGTA
CAATAAAAGATATGTATGAATGCATCAGTAGCTGAAAAAAAAAAAAAA

FIGURE 52

MQDEDGYITLNIKTRKPALVSVGPASSSWWRVMALILLILCVGMVVGLVALGIWSVMQRNY
LQDENENRTGTLQQLAKRFCQYVVKQSELKGTFKGHKCSPCDTNWRYYGDSYGFRRHNL
WEESKQYCTDMNATLLKIDNRNIVEYIKARTHLIRWVGLSRQKSNEVWKWEDGSVISENMF
EFLEDGKGNMNCAYFHNGKMHPTFCENKHYLMCERKAGMTKVDQLP

FIGURE 53

CCCTGACCTCCCTGAGCCACACTGAGCTGGAAGCCGAGAGGTCATCCTGGAGCATGCCACCGCGGGGAGCAG
ACAACCTCCCAGGTAAGCTGGGAGCAAGACCTGAAGCTGTTTCTTCAGGAGCCTGGTGATTTTCCCCACCCC
ACCTCAGCAGTTTCAGCCAGCAGGGACTGATCAGGTGTGTCTCGAGTGGGGAGCAGAAGGCGTGGCTGGCA
AGAGTGGCCTGGAGAAAGAGGTTTCAGCGCTTGACCGAGCTGCCCGTGACTACAAGATCCAGAACCATGGG
CATCGGGTGGAGTGGGGGGGCAGGTGTCTGTGCACCTTCTTGTCTCAGCAAGAAGAGCTGAGAGAGGGGAT
CTTGGAGCCATTGAGGGTGTCTAGGAGCTACAGAGGGGAGGGAAAGGTATTTTAAGGTAACAGTGTGGCACAAT
AGTTAAGAGCACAGTTTTTGGAGCTAGACCGACATAGGTTCAAATTTCTTCTGTCTTCTTAGTTCTGTAGC
CCCAGGTAAGGGAGTGACTTAACCTCTCTGGACTTCAATTTCTCTCATCTAAAGTAGGGCCAATAATAGCACC
CACCTCATAGGGAAGATTAAATGACATAATGTATGTGATGCAACTAGCAAAGTACCAGTCCCATAGTAAGTCAT
GCCCCACAGTATTTCCACCCACCCCTGTTCTCTGCCCTTCCCAACCAGGTAAGTCAACGACTGGAGCAGAGGCGG
CAGCAGGCTTCAGAGCGGGAGGCTCCAAGCATAGAACAGAGGTTACAGGAAGTGCGAGAGAGCATCCGCCGGGC
ACAGGTGAGCCAGGTGAAGGGGGCTGCCCGGCTGGCCCTGCTGCAGGGGGCTGGCTTAGATGTGGAGCGCTGGC
TGAAGCCAGCCATGACCCAGGCCAGGATGAGGTGGAGCAGGAGCGCGGCTCAGTAGGCTCGGCTGTCCAG
AGGGACCTCTCTCAACCGCTGAGGATGCTGAGCTTTCTGACTTTGAGGAATGTGAGGAGACGGGAGAGCTCTT
TGAGGAGCCTGCCCCCAAGCCTGGCCACGAGGGCCCTCCCCTGCCCTGCACACGTGGTATTTTCGCTATCAGG
CAGGGCGTGAGGATGAGCTGACAATCACGGAGGGTGAGTGGCTGGAGGTCATAGAGGAGGGAGATGCTGACGAA
TGGGTCAAGGCTCGGAACACAGCAGCGGAGGTAGGCTTTGTCCCTGAGCGATATCTCAACTTCCCGGACCTCTC
CCTCCAGAGAGCAGCCAAGACAGTGACAATCCCTGCGGGGAGAGCCCAAGCATTCCTGGCAGAGGCCCTGT
ACAGCTACACCGGACAGAGTGACAGAGGAGCTGAGCTTCCCTGAGGGGGCACTCATCCGTCTGCTGCCCGGGCC
CAAGATGGAGTAGATGACGGCTTCTGGAGGGGAGAAATTTGGGGGCGGTGTTGGGGTCTTCCCCTCCCTGCTGGT
GGAAGAGCTGCTTGGCCCCCAGGGCCACCTGAACCTCTCTGACCTGAACAGATGCTGCCGTCCCCTTCTCCTC
CCAGCTTCTCCCCACCTGCACCTACCTCTGTGTGGATGGGGCCCTGCACTTCTCTGTCATGACCTATCTAGGGTGGTGAA
CTGGACTTCCCTGGGTCTCTGGACATGATGGCACCTCGACTCAGGCCGATGCGTCCACCACTCCCCCGGGC
TAAAGCCCCGATCCTGGCCACCCAGATCCCCTCACCTGAAGGCCAGGGAAGCCTTGACCCCCAGTGATGCTGC
TGTCCCTATCTTCAAGCTGTGACACCACACCATCAATGATCCAGAGCAACACAGCCAAAGCTGGAATCGCCCT
TATTTCCACCTCACCTCCAAGGGTGGAACTTGCCCTTCCCATTCTAGAGCTGGAACCACTCCTTTTTTT
CCCATTGTTCTATCATCTCTAGGACCGGAACCTACTACCTTCTCTTCTGTCTATGACCTATCTAGGGTGGTGAA
TGCTTGAATCTCTGGGGTGGAAACCATCCATCAAGGTCTCTAGTAGTTCTGGCCACCTCTTTCCCACCCCT
GGCTCCATGACCCACCCACTCTGGATGCCAGGGTCACTGGGGTGGGGCTGGGGAGAGGAACAGGCCCTTGGGAA
TCAGGAGCTGGAGCCAGGATGCGAAGCAGCTGTAATGGTCTGAGCGGATTTATTGACAATGAATAAGGGCACG
AAGGCCAGGCCAGGGCTGGGCCCTCTTGTGCTAAGAGGCGAGGGGCCCTACGGTGCTATTGCTTTAGGGGCCCA
CCAGGGCAGGGGCTGCTCCCAGCTGCCACGCTCTATCATATGAGAGCGAGGTGTTGGGGAAGCGGGCAGGC
AGCCTGTTGAGGCGAGGGGAAGGAGAAGAGACTGAGGGGCTGTGACCTCTCCTGAGGCCCCAGCCTGAGACTG
TGCAACTCCAGGTGGAAGTAGAGCTGGTCCCTCAGCTGGGGGGCAGTGCTGTCCAGTGGAGGGGAGGGCTTTCA
CGCCACCCACCCCTGGCCCTGCCAGCTGGTAGTCCATCAGCACAATGAAGGAGACTTGGAGAAGAGGAAGAA
TAACACTGTTGCTTCTTCAAGCTGTGTCAGCTTTTCCCCTGGGGCTCCAGGACCTTCCCTACCTCCACCA
CCAAACCAAGGGATTTATAGCAAAGGCTAAGCCTGCAGTTTACTCTGGGGGTTTCAGGGAGCCGAAAGGCTTAAA
TAGTTTAAGTAGGTGATGGGAAGATGAGATTACCTCATTTAGGGCTCAGGCAGACTCACCTCACATACTCCCTG
CTCCCTGTGGTAGAGACACCTGAGAGAAAGGGGAGGGGTCAACAATGAGAGACCAGGAGTAGGTCTTATCAGTG
CCCCCAGAGTAGAGAGCAATAAGAGCCAGCCAGTGCAGTCCCGGCTGTGTTTCTTACCTGGTGATCAGAA
GTGTCTGGTTTGTGCTGGCTGCCATTGCTCTTGTAGTGGGCAGCCCTGGGGCTTGGGCCCCCTCCCTCCGGCCCT
CAGTGTGGCTCTGCAGAAGCTCTGGGGTCCCTTCAAGTGCACGAGGGGTAGGCTGCTGTCCCTGAGTCCCTC
CATTCGTACTGGGGGCTGGCTAGGACCTGGGGCTGTGGCCCTCTCAGGGGGCAGCCTCTCCATGGCAGGCATC
CCTGCCCTGGGGCTGCCCTCCCCAGACCCCTGACCAACCCCTGGGTCTGTCCCCCACCAGAGCCCCAGCTCCT
GTCTGTGGGGAGCCATCACGGTGTTCGTGCACTCCATAGCGCTTCTCAATGTGTGTCACCCGGAACCTGGGAG
GGGAGGGAACACTGGGGTTTAGGACCACAACCTCAGAGGCTGCTTGGCCCTCCCTCTGACCAGGGACATCCTGA
GTTTGTGGCTACTTCCCTCTGGCCTAAGGTAGGGGAGGCCTTCTCAGATTGTGGGGCACATTGTGTAGCCTGA
CTTCTGTGAGCTCCAGTCCAGGAGGAAAGAGCCAAGGCCACTTTTGGGATCAGGTGCTGATCACTGGGC
CCCCTACCTCAGCCCCCTTTCCCTGGAGCACCTGCCACCTGCCACAGAGAACACAGTGGTCTCCCCTGTC
CGGGGGCGGCTTTTCTCTTCTTGGAGCGTCCCTGACGGAACAAGTGGAGGCTCTTGTCTGCGGCTGCAATGGAT
GCAAGGGGCTGCAGAGCCAGGTGCACTGTGTGATGATGGGAGGGGGCTCCGTCTGCAGGCTGGAGGTGGCAT
CCACACTGGACAGCAGGAGGAGGGAGTGAGGGTAACATTTCCATTTCCCTTCATGTTTGTCTTACGTTCT
TTCAGCATGCTCCTTAAAAACCCAGAGCCCCAATTTCCCCAGCCCCATTTTTTCTTGTCTTATCTAATAAA
CTCAATATTAAG

FIGURE 54

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA73401

><subunit 1 of 1, 370 aa, 1 stop

><MW: 40685, pI: 4.53, NX(S/T): 0

MQLAKYQSHSKSCPTVFPPTPVLCLPNQVLQRLEQRRQQASEREAPSIEQRLQEVRESIRRAQVSQVKGAAARLA
LLQGAGLDVERWLKPAMTQAQDEVEQERRLSEARLSQRDLSPATAEDAELSDFEECEETGELFEEPAPQALATRA
LPCPAHVVFVRYQAGREDELTITEGEWLEVIEEGDADEWVKARNQHGEVGFVPERYLNFDDLSPSSQSDNPC
GAEPFAFLAQALYSYTGQSAEELSPFEGALIRLLPRAQDGVDDGFWRGEFGGRVGVFPSSLVEELLGPPGPPPEL
SDPEQMLPSPSPSPSPSPAPTSLVDGPPAPVLPDGDALDFPGFLDMMAPRLRPMRPPPPPPAKAPDPGHDPDLT

FIGURE 55

CCCACGCGTCCGCCCACGCGTCCGGGTGCCACTCGCGCGCCGGCCGCGCTCCGGGCTTCTCTTTCCCTCCGAC
GCGCCACGGCTGCCAGACATTCCGGCTGCCGGGTCTGGAGAGCTCCCCGAACCCCTCCGCGGAGAGGAGCGAG
GCGGCGCCAGGGTGGCCCCCGGGCGCGCTTGGTCTCGGAGAAGCGGGGACGAGGCCGAGGATGAGCGACTGA
GGGCGACGCGGGCACTGACGCGAGTTGGGGCCGCGACTACCGGCAGCTGACAGCGCGATGAGCGACTCCCCAGA
GACGCCCTAGCCCGGTGTGCGGCCAGGCGGAGCGCGCAGGTGGGGCTGGGCTGTTAGTGGTCCGCCCCACGCG
GGTCGCGCGCCGGCCAGGATGGGCGCTGGCAACCCGGGCCCCGCGCCGCGCTGCTACCCCTGCGCCCGCTGC
GAGCCCGGCGTCCGGCCCGCGCCCTGCGCTCATGGACGGCGGCTCCCGGCTGGCGGGCGCGCGCCCCGGGCTG
TGAATGCGACTCGCCCCCTCGGCCGCGCTCCCCGCCCGCCCGCCCGGGACGTGGTAGGGGATGCCAGCTCC
ACTGCGATGGCAGTTGGCGCGCTCTCCAGTTCCTCCTGGTCACTGCTGCTGATGGTGGCTCTGTGCAGTCC
GAGCATCCCGCTGGAGAAGCTGGCCCAGGCACAGAGCAGCCGGGCCAGGAGAAGCGTGAGCACGCCACTCGGG
ACGGCCCCGGGGCGGGTGAACGAGCTCGGGCGCCCGCGAGGGACGAGGGCGGCAGCGGCCGGGACTGGAAGAGC
AAGAGCGGCCGTGGGCTCGCCGGCCGTGAGCCGTGGAGCAAGCTGAAGCAGGCCTGGGTCTCCAGGGCGGGG
CGCCAAGGCCGGGGATCTGCAGGTCCGGCCCCCGGGGACACCCCGCAGGCGGAAGCCCTGGCCCGAGCCGCCC
AGGACCGGATTGGCCCCGAACTCGCGCCACGCCGAGCCACCCGAGGAGTACGTGTACCCGGACTACCGTGGC
AAGGGCTGCGTGGACGAGAGCGGCTTCGTGTACGCGATCGGGGAGAAGTTCGCGCCGGGCCCTCGGCCGCCC
GTGCCGTGTGCACCGAGGAGGGGCGCTGTGCGCGCAGCCCGAGTGCCCGAGGCTGCACCCGCGCTGCATCCACG
TCGACACGAGCCAGTGCTGCCCAGTGCAAGGAGAGGAAGAACTACTGCGAGTTCGGGGCAAGACCTATCAG
ACTTTGGAGGAGTTCGTGGTGTCTCCATGCGAGAGGTGTGCTGTGAAGCCAACGGTGAGGTGCTATGCACAGT
GTCAGCGTGTCCCCAGACGGAGTGTGTGGACCTGTGTACGAGCCTGATCAGTGCTGTCCCATCTGCAAAAATG
GTCCAACTGCTTTGCAGAAACCGCGGTGATCCCTGCTGGCAGAGAAGTGAAGACTGACGAGTGACCCATATGC
CACTGTACTTATGAGGAAGGCACATGGAGAATCGAGCGGCAGGCCATGTGCACGAGACATGAATGCAGGCAAT
GTAGACGCTTCCAGAACACAACTCTGACTTTTCTAGAACATTTTACTGATGTGAACATTCTAGATGACTCT
GGGAATATCAGTCAAAGAAGACTTTTGATGAGGAATAATGGAAAATTGTTGGTACTTTTCCTTTTCTTGATAA
CAGTTACTACAACAGAAGGAAATGGATATATTTCAAACATCAACAAGAACTTTGGGCATAAAATCCTTCTCTA
AATAAATGTGCTATTTTCACAGTAAGTACACAAAAGTACACTATTATATATCAAATGTATTTCTATAATCCCTC
CATTAGAGAGCTTATATAAGTGTTTTCTATAGATGCAGATTAAAAATGCTGTGTGTCAACCGTCAAAAAAAA
AAAAAAAAAAAAAAAAAAAA

FIGURE 56

MPSSSTAMAVGALSSSLVTCCLMVALCSPSIPLEKLAQAPEQPGQEKREHATRDGPGRVNELGRPARDEGGSGR
DWKSKSGRGLAGREPWSKLQAWVSQGGGAKAGDLQVRPRGDTQAEALAAAQDAIGPELAPTPEPPEEYVYP
DYRGKGCVDSESGFVYAIGKFAFGPSACPCLCTEEGPLCAQPECPRLHPRCIHVDTSQCCPQCKERKNYCEFRG
KTYQTLEEFVVSPCRRCRCEANGEVLCTVSACPQTECVDPVYEPDQCCPICKNGPNCFAETAVIPAGREVKTDE
CTICHCTYEETWRIERQAMCTRHECRQM

Important features:**Signal peptide:**

amino acids 1-27

Transmembrane domain:

amino acids 11-30

Glycosaminoglycan attachment site.

amino acids 80-83

N-myristoylation sites.

amino acids 10-15, 102-107, 103-108

Cell attachment sequence.

amino acids 114-117

EGF-like domain cysteine pattern signature.

amino acids 176-187

FIGURE 57

GGAGGCGGAGGCCGCGGCGAGCCGGGCGGAGCAGTGAGGGCCCTAGCGGGGCCGAGCGGGGCCCGGGGCCCT
AAGCCATTCCTGAAGTCATGGGCTGGCCAGGACATTGGTGACCCGCCAATCCGGTATGGACGACTGGAAGCCCA
GCCCCCTCATCAAGCCCTTTGGGGCTCGGAAGAAGCGGAGCTGGTACCTTACCTGGAAGTATAAACTGACAAAC.
CAGCGGGCCCTGCGGAGATTCTGTCTAGACAGGGGCCGTGCTTTTCTCTGCTGGTGAAGTGTCAATTGTCAATATCAA
GTTGATCCTGGACACTCGGCGAGCCATCAGTGAAGCCAATGAAGACCCAGAGCCAGAGCAAGACTATGATGAGG
CCCTAGGCCCGCTGGAGCCCCACGGCGCAGAGGCAGTGGTCCCCGGCGGGTCTCTGGACGTAGAGGTGTATTCA
AGTCGCAGCAAAGTATATGTGGCAGTGGATGGCACCACGGTGTCTGGAGGATGAGGCCCGGGAGCAGGGCCGGGG
CATCCATGTCTATTGTCTCAACCAGGCCACGGGCCACGTGATGGCAAACGTGTGTTTGACACGTACTCACCTC
ATGAGGATGAGGCCATGGTGTCTATTCTCAACATGGTAGCGCCCCGGCCGAGTGTCTCATCTGCACTGTCAAGGAT
GAGGGCTCCTTCCACCTCAAGGACACAGCCAAGGCTCTGCTGAGGAGCCTGGGCAGCCAGGCTGGCCCTGCCT
GGGCTGGAGGGACACATGGGCCTTCGTGGGACGAAAAGGAGGTCTGTCTTCGGGGAGAAACATTCTAAGTCAC
CTGCCCTCTCTTCTGGGGGACCCAGTCTGTCTGAAGACAGATGTGCCATTGAGCTCAGCAGAAGAGGCAGAG
TGCCACTGGGCAGACACAGAGCTGAACCGTCGCCCGGGCGCTTCTGCAGCAAAGTTGAGGGCTATGGAAGTGT
ATGCAGCTGCAAGGACCCACACCCATCGAGTTCAGCCCTGACCCACTCCCAGACAACAAGGTCTCAATGTGC
CTGTGGCTGTCTATTGCAGGAACCGACCCAATTACCTGTACAGGATGCTGCGCTCTCTGCTTTAGCCAGGGG
GTGTCTCTCAGATGATAACAGTTTTTCATTGACGGCTACTATGAGGAACCCATGGATGTGGTGGCACTGTTTGG
TCTGAGGGGCATCCAGCATACTCCCATCAGCATCAAGAATGCCCGCGTGTCTCAGCACTACAAGGCCAGCCTCA
CTGCCACTTTCAACCTGTTCCTGGAGGCCAAGTTTGCTGTGGTTCTGGAAGAGGACCTGGACATTGTGTGGAT
TTTTTCAGTTTCCTGAGCCAATCCATCCACCTACTGGAGGAGGATGACAGCCTGTACTGCATCTCTGCCTGGAA
TGACCAGGGGTATGAACACACGGCTGAGGACCCAGCACTACTGTACCGTGTGGAGACCATGCCTGGGCTGGGCT
GGGTGCTCAGGAGGTCTTGTACAAGGAGGAGCTTGAGCCCAAGTGGCCTACACCGGAAAAGCTCTGGGATTGG
GACATGTGGATGCGGATGCCTGAACAACGCCGGGCGGAGAGTGCATCATCCCTGACGTTTCCCGATCCTACCA
CTTTGGCATCGTCGGCTCAACATGAATGGCTACTTTACGAGGCCTACTTCAAGAAGCACAAAGTTCAACACGG
TTCCAGGTGTCCAGCTCAGGAATGTGGACAGTCTGAAGAAAGAAGCTTATGAAGTGAAGTTCACAGGCTGCTC
AGTGAGGCTGAGGTTCTGGACCACAGCAAGAACCCTTGTGAAGACTCTTTCTCTGCCAGACACAGAGGGCCACAC
CTACGTGGCCTTTATTTCGAATGGAGAAAGATGATGACTTCACCACCTGGACCCAGCTTGCCAAGTGCCTCCATA
TCTGGGACCTGGATGTGCGTGGCAACCATCGGGGCTGTGGAGATTGTTTCGGAAGAAGAACCCTTCTGGTG
GTGGGGGTCCCGGCTTCCCCCTACTCAGTGAAGAAGCCACCCTCAGTCACCCCAATTTTCTGGAGCCACCCCC
AAAGGAGGAGGGAGCCCCAGGAGCCCCAGAACAGACATGAGACCTCCTCCAGGACCCTGCGGGGCTGGGTACTG
TGTACCCCCAGGCTGGCTAGCCCTTCCCTCCATCCTGTAGGATTTTGTAGATGCTGGTAGGGGCTGGGGCTACC
TTGTTTTTAACATGAGACTTAATTACTAACTCCAAGGGGAGGGTTCCCTGTCTCCAACACCCCGTTCTGAGTT
AAAAGTCTATTTATTTACTTCTTGTGGAGAAGGGCAGGAGAGTACCTGGGAATCATTACGATCCCTAGCAGC
TCATCCTGCCCTTTGAATACCCTCACTTTCCAGGCCTGGCTCAGAATCTAACCTATTTATTGACTGTCTGAGG
GCCTTGAAAACAGGCCGAACCTGGAGGGCCTGGATTTCTTTTGGGCTGGAATGCTGCCCTGAGGGTGGGGCTG
GCTCTTACTCAGGAACTGCTGTGCCCCAACCCATGGACAGGCCAGCTGGGGCCCATGCTGACACAGACTCA
CTCAGAGACCCTTAGACACTGGACCAGGCCTCCTCTCAGCCTTCTCTTGTCCAGATTTCCAAAGCTGGATAAG
TTGGTCATTGATTAAAAAAGGAGAAGCCCTCTGGGAAAAAATAAAAAAAAAAAAAAAAAA

FIGURE 58

```
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA61185
><subunit 1 of 1, 660 aa, 1 stop
><MW: 75220, pI: 6.76, NX(S/T): 0
MDDWKPSPLIKPFGARKKRSWYLTWKYKLTNQALRRFCQTGAVLFLLVTIVVNIKLILDTRRAISEANEDPEP
EQDYDEALGRLEPPRRRGSGPRRVLDVEVYSSRSKVYVAVDGTTVLEDEAREQGRGIHVIVLNQATGHVMAKRV
FDTYSPEHEAMVLFNLMVAPGRVLICTVKDEGSFHLKDTAKALLRSLGSQAGPALGWRDTWAFVGRKGGPVFG
EKHSKSPALSSWGDVLLKTDVPLSSAEEAECHWADTELNRRRRRFFCSKVEGYGSVCCKDPTPIEFSPDPLPD
NKVLNVPVAVIAGNRPNYLYRMLRSLLSAQGVSPQMITVFIIDGYEPEMDVVALFGLRGIQHTPISIKNARVSQ
HYKASLTATFNLFPFAKFAVVLEEDLDIAVDFFSFLSQSIHLLEEDDSLYCISAWNDQGYEHTAEDPALLYRVE
TMPGLGWVLRRLSYKEELEPKWPTPEKLWDWMWMMRMPEQRRGRECIIPDVSRSYHFGIVGLNMNGYFHEAYFK
KHKENTVPGVQLRNVDLSLKEAYEVEVHRLLSAEVLDHSKNPCEDSFLPDTEGHTYVAFIRMEKDDDDFTTWTQ
LAKCLHIWDLVVRGNHRLWRLFRKKNHFLVVGVPASPYSVKKPPSVTPIFLEPPPKEGAPGAPEQT
```

Important features of the protein:

Transmembrane domain:

amino acids 38-55

Homologous region to Mouse GNT1

amino acids 229-660

FIGURE 59

GGTTCCTGGGCGCTCTGTTACACAAGCAAGATACAGCCAGCCCCACCTAATTTTGTTCCTCC
TGGCACCCCTCCTGCTCAGTGGGACATTGTACACTTAACCCATCTGTTTTCTCTAATGCAC
GACAGATTCCTTTTCTAGACAGGACAACCTGTGATATTTTCTGTTCTGATTGTAAATACCTCCT
AAGCCTGAAGCTTCTGTTACTAGCCATTGTGAGCTTCTGTTTCTTCATCTGCAAAATGGGC
ATAATACAATCTATTCTTGCCACATCAAGGGATTGTTATTCCTTTAAAAAAAACCAATAC
CAAAGAAGCCTACAATGTTGGCCTTAGCCAAAATTCTGTTGATTTCAACGTTGTTTTATTCT
ACTTCTATCGGGGAGCCATGGAAAAGAAAATCAAGACATAAACACAACACAGAACATTGCA
GAAGTTTTTTAAACAATGGAAAATAAACCTATTTCTTTGGAAAGTGAAGCAAACCTTAAACT
CAGATAAAGAAAATATAACCACCTCAAATCTCAAGGCGAGTCATTCCCCTCCTTTGAATCT
ACCCAACAACAGCCACGGAATAACAGATTTCTCCAGTAACCTCATCAGCAGAGCATTTCTTTG
GGCAGTCTAAAACCCACATCTACCATTTCCACAAGCCCTCCCTTGATCCATAGCTTTGTTT
CTAAAGTGCCTTGAATGCACCTATAGCAGATGAAGATCTTTTGCCCATCTCAGCACATCC
CAATGCTACACCTGCTCTGTCTTCAGAAAACCTTCACTTGGTCTTTGGTCAATGACACCGTG
AAAACCTCCTGATAACAGTTCCATTACAGTTAGCATCCTCTCTTCAGAACCAACTTCTCCAT
CTGTGACCCCTTGATAGTGGAAACCAAGTGGATGGCTTACCACAAACAGTGATAGCTTCAC
TGGGTTTACCCCTTATCAAGAAAAACAACCTCTACAGCCTACCTTAAAATTACCAATAAT
TCAAAACTCTTTCCAAATACGTGAGATCCCCAAAAGAAAATAGAAATACAGGAATAGTAT
TCGGGGCCATTTTAGGTGCTATTCTGGGTGTCTCATTGCTTACTCTGTGGGCTACTTGTT
GTGTGGAAAAGGAAAACGGATTCATTTTCCCATCGGCGACTTTATGACGACAGAAATGAA
CCAGTTCTGCGATTAGACAATGCACCGGAACCTTATGATGTGAGTTTTGGGAATTCTAGCT
ACTACAATCCAACCTTTGAATGATTCAGCCATGCCAGAAAGTGAAGAAAATGCACGTGATGG
CATTCCTATGGATGACATACCTCCACTTCGTACTTCTGTATAGAACTAACAGCAAAAAGGC
GTTAAACAGCAAGTGTCTATCATCTACATCCTAGCCTTTTGACAAATTCATCTTTCAAAGGTTA
CACAAAATTACTGTCACGTGGATTTTGTCAAGGAGAATCATAAAAGCAGGAGACCAGTAGC
AGAAATGTAGACAGGATGTATCATCAAAGGTTTTCTTTCTTACAATTTTTGGCCATCCTG
AGGCATTTACTAAGTAGCCTTAATTTGTATTTTAGTAGTATTTCTTAGTAGAAAATATTT
GTGGAATCAGATAAACTAAAAGATTTTACCATTACAGCCCTGCCTCATAACTAAATAATA
AAAATTATTCCACCAAAAATTCTAAAACAATGAAGATGACTCTTTACTGCTCTGCCTGAA
GCCCTAGTACCATAATTCAAGATTGCATTTTCTTAAATGAAAATTGAAAGGGTGCTTTTTTA
AAGAAAATTTGACTTAAAGCTAAAAGAGGACATAGCCCAGAGTTTCTGTTATTGGGAAAT
TGAGGCAATAGAAATGACAGACCTGTATTCTAGTACGTTATAATTTCTAGATCAGCACAC
ACATGATCAGCCCACTGAGTTATGAAGCTGACAATGACTGCATTCAACGGGGCCATGGCAG
GAAAGCTGACCCTACCCAGGAAAGTAATAGCTTCTTTAAAAGTCTTCAAAGGTTTTGGGAA
TTTTAACTTGTCTTAATATATCTTAGGCTTCAATTATTTGGGTGCCTTAAAACTCAATGA
GAATCATGGT

FIGURE 60

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA58732

><subunit 1 of 1, 334 aa, 1 stop

><MW: 36294, pI: 4.98, NX(S/T): 13

MLALAKILLISTLFYSLLSGSHGKENQDINTTQNI AEVFKTMENKPISLESEANLNSDKEN
ITTSNLKASHSPPLNLPNNSHGITDFSSNSSAEHSLGSLKPTSTISTSPPLIHSFVSKVPW
NAPIADEDLLPISAHPNATPALSSNF TWSLVNDTVKTPDNSSITVSILSSEPTSPSVTPL
IVEPSGWLTTNSDSFTGFTPYQEKTTLQPTLKFTNNSKLF PNTSDPQKENRNTGIVFGAIL
GAILGVSLTLVGYLLCGKRKTDSFSHRRLYDDRNEPVLRLDNAPEPYDVSFGNSSYYNPT
LNSAMP ESEENARDGIPMDDIPPLRTSV

Signal peptide:

amino acids 1-23

Transmembrane domain:

amino acids 235-262

N-glycosylation site.

amino acids 30-34, 61-65, 79-83, 90-94, 148-152, 155-159,
163-167, 218-222, 225-229, 298-302, 307-311

FIGURE 61

AGAGAAAGAAGCGTCTCCAGCTGAAGCCAATGCAGCCCTCCGGCTCTCCGCGAAGAAGTTCCCTGCCCCGATGA
GCCCCCGCCGTGCGTCCCCGACTATCCCCAGGCGGGCGTGGGGCACCGGGCCCAGCGCCGACGATCGCTGCCGT
TTTGCCCTTGGGAGTAGGATGTGGTGAAAGGATGGGGCTTCTCCCTTACGGGGCTCACAATGGCCAGAGAAGAT
TCCGTGAAGTGTCTGCGCTGCCTGCTCTACGCCCTCAATCTGCTCTTTTGGTTAATGTCCATCAGTGTGTGGC
AGTTTCTGCTTGGATGAGGGACTACCTAAATAATGTTCTCACTTTAACTGCAGAAACGAGGGTAGAGGAAGCAG
TCATTTTGACTTACTTTCCTGTGGTTCATCCGGTCATGATTGCTGTTTGCTGTTTCCTTATCATTGTGGGGATG
TTAGGATATTGTGGAACGGTGAAAAGAAATCTGTTGCTTCTTGCTGCTGTTTGGAAAGTTTGCTTGTCAATTTT
CTGTGTAGAACTGGCTTGTGGCGTTTGGACATATGAACAGGAACCTTATGGTTCAGTACAATGGTCAGATATGG
TCACTTTGAAAGCCAGGATGACAAATTATGGATTACCTAGATATCGGTGGCTTACTCATGCTTGAATTTTTTT
CAGAGAGAGTTTAAAGTGTGTGGAGTAGTATATTCTCACTGACTGGTTGGAATGACAGAGATGGACTGGCCCCC
AGATTCTGCTGTGTGTAGAGAATCCCAGGATGTTCCAAACAGGCCACCAGGAAGATCTCAGTGACCTTTATC
AAGAGGGTGTGGGAAGAAAATGTATTCTTTTTTGAGAGGAACCAACAACCTGCAGGTGCTGAGGTTTCTGGGA
ATCTCCATTGGGGTGACACAAATCCTGGCCATGATTCTCACCATTACTCTGCTCTGGGCTCTGTATTATGATAG
AAGGGAGCTGGGACAGACCAATGATGTCTTGAAGAATGACAACTCTCAGCACCTGTCTGCTCCCTCAGTAG
AACTGTTGAAACCAAGCCTGTCAAGAATCTTTGAACACACATCCATGGCAAACAGCTTTAATACACACTTTGAG
ATGGAGGAGTTATAAAAAGAAATGTACAGAAGAAAACCACAACTTGTTTTATTGGACTTGTGAATTTTTGAG
TACATACATGTGTTTTCAGAAATATGTAGAAATAAAATGTTGCCATAAAATAACACCTAAGCATATACTATTCT
TATGCTTTAAAATGAGGATGGAAAAGTTTCATGTCTAAGTACCACCTGGACAATAATTGATGCCCTTAAAAT
GCTGAAGACAGATGTCTATCCCACTGTGTAGCCTGTGTATGACTTTTACTGAACACAGTTATGTTTTGAGGCAG
CATGGTTTGATTAGCATTTCGCATCCATGCAAACGAGTCACATATGGTGGGACTGGAGCCATAGTAAAGGTTG
ATTTACTTCTACCACTAGTATATAAAGTACTAATTAAATGCTAACATAGGAAGTTAGAAAATACTAATAACTT
TTATTACTCAGCGATCTATTCTTCTGATGCTAAATAAATTATATATCAGAAAACCTTCAATATTGGTGACTACC
TAAATGTGATTTTTGCTGGTTACTAAAATATTCTTACCACTTAAAAGAGCAAGCTAACACATTGTCTTAAGCTG
ATCAGGGATTTTTTGTATATAAGTCTGTGTAAATCTGTATAATTCACTCGATTTCAGTTCTGATAATGTTAAG
AATAACCATTATGAAAAGGAAAATTTGTCTGTATAGCATCATTATTTTAGCCTTTCCTGTTAATAAAGCTTT
ACTATTCTGTCTGGGCTTATATTACACATATAACTGTTATTTAAATACTTAACCACTAATTTGAAAATTACC
AGTGTGATACATAGGAATCATTATTGAGAATGTAGTCTGGTCTTTAGGAAGTATTAATAAGAAAATTTGCACAT
AACTTAGTTGATTGAGAAAGGACTTGTATGCTGTTTTCTCCCAAATGAAGACTCTTTTGGACACTAAACACTT
TTTAAAAGCTTATCTTTGCCTTCTCCAAACAAGAAGCAATAGTCTCCAAGTCAATATAAATTCTACAGAAAAT
AGTGTCTTTTTCTCCAGAAAATGCTTGTGAGAATCATTAAAACATGTGACAATTTAGAGATTCTTTGTTTTA
TTTCACTGATTAATATACTGTGGCAAATTACACAGATTATTAAATTTTTTACAAGAGTATAGTATATTTATTT
GAAATGGGAAAAGTGCAATTTACTGTATTTTGTGTATTTTGTATTCTCAGAAATATGGAAAGAAAATTTAAA
TGTGTCAATAAATATTTTCTAGAGAGTAA

FIGURE 62

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA68880

><subunit 1 of 1, 305 aa, 1 stop

><MW: 35383, pI: 5.99, NX(S/T): 0

MAREDSVKCLRCLLYALNLLFWLMSISVLAVSAWMRDYLNNVLTTLTAETRVEEAVILTYFP
VVHPVMIAVCCFLIIVGMLGYCGTVKRNLLLLAWYFGSLLVIFCVELACGVWTYEQELMVP
VQSDMVTLKARMTNYGLPRYRWLTHAWNFFQREFKCCGVVYFTDWLEMTMDWPPDSCCV
REFPGCSKQAHQEDLSDLYQEGCGKMYSFRLRGTKQLQVLRFLGISIGVTQILAMILTITL
LWALYYDRREPGETDQMMSLKNDNSQHLSCPSVELLKPSLSRIFEHTSMANSFNTHFEMEEL

Signal peptide:

amino acids 1-33

Transmembrane domains:

amino acids 12-35, 57-86, 94-114, 226-248

FIGURE 63

GGAAAACTGTTCTCTTCTGTGGCACAGAGAACCCTGCTTCAAAGCAGAAGTAGCAGTTCC
GGAGTCCAGCTGGCTAAAACTCATCCCAGAGGATAATGGCAACCCATGCCTTAGAAATCGC
TGGGCTGTTTCTTGGTGGTGTGGAATGGTGGGCACAGTGGCTGTCACTGTCATGCCTCAG
TGGAGAGTGTCGGCCTTCATTGAAAACAACATCGTGGTTTTTGAAAACCTTCTGGGAAGGAC
TGTGGATGAATTGCGTGAGGCAGGCTAACATCAGGATGCAGTGCAAAATCTATGATTCCCT
GCTGGCTCTTCTCCGGACCTACAGGCAGCCAGAGGACTGATGTGTGCTGCTTCCGTGATG
TCCTTCTTGGCTTTCATGATGGCCATCCTTGGCATGAAATGCACCAGGTGCACGGGGGACA
ATGAGAAGGTGAAGGCTCACATTCTGCTGACGGCTGGAATCATCTTCATCATCACGGGCAT
GGTGGTGCTCATCCCTGTGAGCTGGGTTGCCAATGCCATCATCAGAGATTTCTATAACTCA
ATAGTGAATGTTGCCCAAAAACGTGAGCTTGGAGAAGCTCTCTACTTAGGATGGACCACGG
CACTGGTGCTGATTGTTGGAGGAGCTCTGTTCTGCTGCGTTTTTTGTTGCAACGAAAAGAG
CAGTAGCTACAGATACTCGATACCTTCCCATCGCACAAACCCAAAAAAGTTATCACACCGGA
AAGAAGTCACCGAGCGTCTACTCCAGAAGTCAGTATGTGTAGTTGTGTATGTTTTTTTAAC
TTTACTATAAAGCCATGCAAATGACAAAAATCTATATTACTTTCTCAAAATGGACCCCAA
GAACTTTGATTTACTGTTCTTAAGTGCCTAATCTTAATTACAGGAAGTGTGCATCAGCTA
TTTATGATTCTATAAGCTATTTTCAAGCAGAAATGAGATATTAAACCAATGCTTTGATTGTTT
TAGAAAGTATAGTAATTTGTTTTCTAAGGTGGTTCAAGCATCTACTCTTTTATCATTTAC
TTCAAAATGACATTGCTAAAGACTGCATTATTTTACTACTGTAATTTCTCCACGACATAGC
ATTATGTACATAGATGAGTGTAACATTTATATCTCACATAGAGACATGCTTATATGGTTTT
ATTTAAAATGAAATGCCAGTCCATTACACTGAATAAATAGAACTCAACTATTGCTTTTCAG
GGAAATCATGGATAGGGTTGAAGAAGGTACTATTAATTGTTTAAAAACAGCTTAGGGATT
AATGTCCTCCATTTATAATGAAGATTAAATGAAGGCTTTAATCAGCATTGTAAAGGAAAT
TGAATGGCTTTCTGATATGCTGTTTTTTAGCCTAGGAGTTAGAAATCCTAATTCTTTATC
CTCTTCTCCCAGAGGCTTTTTTTTTCTTGTGTATTAAATTAACATTTTTTAAACGCAGATA
TTTTGTCAAGGGGCTTTGCATTCAAAGTCTTTTCCAGGGCTATACTCAGAAGAAAGATAA
AAGTGTGATCTAAGAAAAAGTGATGGTTTTAGGAAAGTGAAAATATTTTTGTTTTTGTATT
TGAAGAAGAATGATGCATTTTGACAAGAAATCATATATGTATGGATATATTTTAATAAGTA
TTTGAGTACAGACTTTGAGGTTTCATCAATATAAATAAAAGAGCAGAAAAATATGTCTTGG
TTTTCATTTGCTTACCAAAAAAACAACAACAAAAAAGTTGTCCTTTGAGAACTTCACCTG
CTCCTATGTGGGTACCTGAGTCAAATTTGTCATTTTTGTTCTGTGAAAAATAAATTCCTT
CTTGATACATTTCTGTTTAGTTTTACTAAAATCTGTAAATACTGTATTTTTCTGTTTTATTC
CAAATTTGATGAACTGACAATCCAATTTGAAAGTTTGTGTGCGACGTCTGTCTAGCTTAAA
TGAATGTGTTCTATTTGCTTTATACATTTATATTAATAAATTGTACATTTTTCTAATT

FIGURE 64

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA73735

><subunit 1 of 1, 225 aa, 1 stop

><MW: 24845, pI: 9.07, NX(S/T): 0

MATHALEIAGLFLGGVGMVGTVAVTVMQWRVSAFIENNIVVFENFWEGLWMNCVRQANIR
MQCKIYDSSLALSPDLQAARGLMCAASVMSFLAFMMAILGMKCTRCTGDNEKVKAHILLTA
GIIFIITGMVVLIPVSWVANAIIRDFYNSIVNVAQKRELGEALYLGWTTALVLIVGGALFC
CVFCCNEKSSSYRYSIPSHRTTQKSYHTGKKSPSVYSRSQYV

Signal peptide:

amino acids 1-17

Transmembrane domains:

amino acids 82-101, 118-145, 164-188

FIGURE 65

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGTCTCTGCGGGGAGACGCCAGCCTGC
GTCTGCCATGGGGCTCGGGTTGAGGGGCTGGGGACGTCTCTGCTGACTGTGGCCACCGCC
CTGATGCTGCCCCTGAAGCCCCCGCAGGCTCCTGGGGGGCCCAGATCATCGGGGGCCACG
AGGTGACCCCCACTCCAGGCCCTACATGGCATCCGTGCGCTTCGGGGGCCAACATCACTG
CGGAGGCTTCTGCTGCGAGCCCGCTGGGTGGTCTCGGCCGCCCACTGCTTCAGCCACAGA
GACCTCCGCACTGGCCTGGTGGTGCTGGGCGCCACGTCTGAGTACTGCGGAGCCCACCC
AGCAGGTGTTTGGCATCGATGCTCTCACCACGCACCCCGACTACCACCCCATGACCCACGC
CAACGACATCTGCCTGCTGCGGCTGAACGGCTCTGCTGTCTCTGGGCCCTGCAGTGGGGCTG
CTGAGGCTGCCAGGGAGAAGGGCCAGGCCCCCACAGCGGGGACACGGTGCCGGGTGGCTG
GCTGGGGCTTCGTGTCTGACTTTGAGGAGCTGCCGCTGGACTGATGGAGGCCAAGGTCCG
AGTGCTGGACCCGGACGTCTGCAACAGCTCCTGGAAGGGCCACCTGACACTTACCATGCTC
TGCACCCGCAGTGGGGACAGCCACAGACGGGGCTTCTGCTCGGCCGACTCCGGAGGGCCCC
TGGTGTGCAGGAACCGGGCTCACGGCCTCGTTTCCTTCTCGGGCCTCTGGTGCGGCGACCC
CAAGACCCCCGACGTGTACACGCAGGTGTCCGCCTTTGTGGCCTGGATCTGGGACGTGGTT
CGGCGGAGCAGTCCCCAGCCCGGCCCCCTGCCTGGGACCACCAGGCCCCCAGGAGAAGCCG
CCTGAGCCACAACCTTGCGGCATGCAAATGAGATGGCCGCTCCAGGCCTGGAATGTTCCGT
GGCTGGGCCCCACGGGAAGCCTGATGTTACAGGTTGGGGTGGGACGGGCAGCGGTGGGGCA
CACCCATTCCACATGCAAAGGGCAGAAGCAAACCCAGTAAAATGTAACTGACAAAAAAA
AAAAAAAAAAAAAGAAA

FIGURE 66

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA62845

><subunit 1 of 1, 283 aa, 1 stop

><MW: 30350, pI: 9.66, NX(S/T): 2

MGLGLRGWGRPLLTVATALMLPVKPPAGSWGAIIGGHEVTPHSRPYMASVRFGGQHHC GG
FLLRARWVVSAAHCFSHRDLRTGLVVLGAHVLSTAEPTQQVFGIDALTTHPDYHPMTHAND
ICLLRLNGSAVLGPAVGLLRLLPGRRARPPTAGTRCRVAGWGFVSDFEELPPGLMEAKVRVL
DPDVCNSSWKGHLLTMLCTRSGDSHRRGFCSADSGGPLVCRNRAHGLVSFSGLWCGDPKT
PDVYTQVSAFVAWIWDVVRSSPQPGPLPGTTRPPGEAA

Signal peptide:

amino acids 1-30

CCGCCGCCGCAGCCCGCTACCGCCGCTGCAGCCGCTTTTCGCGGCCCTGGGCCCTCTCGCCGTACGATGCCACACAC
CCTTCAAGCCCCGGGACTTGGTGTTCGCTAAGATGAAGGGCTACCCCTCACTGGCCTGCCAGGATCGACGACATC
GCGGATGGCGCCGTGAAGCCCCACCCAACAAGTACCCCATCTTTTCTTTGGCACACAGAAACAGCCTTCTCT
GGGACCCCAAGGACCTGTTCCTTACGACAAATGTAAAGACAAGTACGGGAAGCCCAACAAGAGGAAAGGCTTCA
ATGAAGGGCTGTGGGAGATCCAGAACAACCCCCACGCCAGTACAGCGCCCCCTCCGCCAGTGAGCTCCTCCGAC
AGCGAGGCCCCCGAGGCCAACCCCGCCGACGGCAGTGACGCTGACGAGGACGATGAGGACCGGGGGGTCTATGGC
CGTCACAGCGGTAAACGCCACAGCTGCCAGCGACAGGATGGAGAGCGACTCAGACTCAGACAAGAGTAGCGACA
ACAGTGGCCTGAAGAGGAAGACGCCCTGCGCTAAAGATGTCTGGTCTCGAAACGAGCCCGAAAGGCCTCCAGCGAC
CTGGATCAGGCCAGCGTGTCCCATCCGAAGAGGAGAACTCGGAAAGCTCATCTGAGTCGGAGAAGACCAGCGA
CCAGGACTTCACACCTGAGAAGAAAGCAGCGGTCCGGGCGCCACGGAGGGGCCCTCTGGGGGGACGGAAAAAAA
AGAAGGCGCCGTACGCTCCGACTCCGACTCCAAGGCCGATTCCGACGGGGCCAAGCCTGAGCCGTGGCCATG
GCGCGGTGCGCGTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCCGACTCCGATGTGTCTGTGAAGAAGCCTCCGAG
GGGCAGGAAGCCAGCGGAGAAGCCTCTCCGAAGCCGCGAGGGCGGAAACCGAAGCCTGAACGGCCTCCGTCCA
GCTCCAGCAGTGACAGTGACAGCGACGAGGTGGACCGCATCAGTGAGTGGAAGCGGCGGGACGAGGCCGCGGAGG
CGCGAGCTGGAGGCCCGCGCGGCGGCGAGAGCAGGAGGAGGAGCTGCGGCGCCTGCGGGAGCAGGAGAAGGAGGA
GAAGGAGCGGAGGCGCGAGCGGGCCGACC CGGGGAGGCTGAGCGGGGCAGCGGCGGCAGCAGCGGGGACGAGC
TCAGGGAGGACGATGAGCCCGTCAAGAAGCGGGGACGCAAGGGCCGGGGCCGGGGTCCCCCGTCTCTCTGTAC
TCCGAGCCCGAGGCCGAGCTGGAGAGAGAGGCCAAGAAATCAGCGAAGAAGCCGAGTCTCAAGCACAGAGCC
CGCCAGGAAACCTGGCCAGAAGGAGAAGAGAGTGCGGCCCCGAGGAGAAGCAACAAGCCAAGCCCGTGAAGGTGG
AGCGGACCCGAAGCGGTCCGAGGGCTTCTCGATGGACAGGAAGGTAGAGAAGAAGAAAGAGCCCTCCGTGGAG
GAGAAGCTGCAGAAGCTGCACAGTGAGATCAAGTTTGCCCTAAAGGTGACAGCCCGGACGTGAAGAGGTGCCT
GAATGCCCTAGAGGAGCTGGGAACCTGACAGGTGACCTCTCAGATCCTCCAGAAGAACAGACGTGGTGGCCA
CCTTGAAGAAGATTGCGCGTTACAAGCGAACAAGGACGTAATGGAGAAGGCAGCAGAAGTCTATACCCGGCTC
AAGTCGCGGGTCTCTCGGCCCAAAGATCGAGGCGGTGCAGAAAGTGAACAAGGCTGGGATGGAGAAGGAGAAGGC
CGAGGAGAAGCTGGCCGGGGAGGAGCTGGCCGGGGAGGAGGCCCCCCAGGAGAAGGCGGAGGACAAGCCAGCA
CCGATCTCTCAGCCCCAGTGAATGGCGAGGCCACATCAAGAAGGGGGAGAGCGCAGAGGACAAGGAGCACGAG
GAGGGTTCGGGACTCGGAGGAGGGGCCAAGGTGTGGCTCCTCTGAAGACCTGCACGACAGCGTACGGGAGGGTCC
CGACCTGGACAGGCCTGGGAGCGACCGGCAGGAGCGCGAGAGGGCACGGGGGGACTCGGAGGCCCTGGACGAGG
AGAGCTGAGCCGCGGGCAGCCAGGCCACGCCCCCGCCGAGCTCAGGCTGCCCTCTCTTCCCCGGCTCGCAG
GAGAGCAGAGCAGAGAACTGTGGGGAACGCTGTGCTGTTTGTATTGTTCCTTGGGTTTTTTTTTCTGCCTA
ATTTCTGTGATTTCCAACCAACATGAATGACTATAACCGGTTTTTTAATGA

FIGURE 68

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA71286

><subunit 1 of 1, 671 aa, 1 stop

><MW: 74317, pI: 7.61, NX(S/T): 0

MPHAFKPGDLVFAKMKGYPHWPARIDDIADGAVKPPPNKYPIFFFGTHETAFLGPKDLFPY
DKCKDKYGKPNKRKGFNEGLWEIQNNPHASYSAPPPVSSSDSEAPEANPADGSDADEDED
RGVMAVTAVTATAASDRMESDSDSDKSSDNSGLKRKTPALKMSVSKRARKASSDLDQASVS
PSEEENSESSSESEKTSQDFTPEKKA AVRAPRRGPLGGRKKKKAPSASDSDSKADSDGAK
PEPVAMARSASSSSSSSSSSSDSDSVKKPPRGRKPAEKPLPKPRGRKPKPERPPSSSSSDS
DSDEVDRISEWKRRDEARRRELEARRRREQEEELRRLREQEKEEKERRRERADRGEAERGS
GGSSGDELREDDEPVKKRGRKGRGRGPPSSSDSEPEAELEAREAKKSAKKPQSSSTEPARKP
GQKEKRVRP EEKQQA KPVKVERTKRSEGFSMDRKVEKKKEPSVEEKLQKLHSEIKFALKV
DSPDVKRCLNALEELGTLQVTSQILQKNTDVVATLKKIRRYKANKDVMKAAEVYTRLKSR
VLGPKIEAVQKVNKAGMEKEKAEKLAG EELAGEEAPQEKAEDKPSTDLSAPVNGEATSQK
GSAEDKEHEEGRDSEEGPRCGSSEDLHDSVREGPDLD RPGSDRQERERARGDSEALDEES

Signal peptide:

amino acids 1-13

FIGURE 69

GAGCGGAGTAAATCTCCACAAGCTGGGAACAAACCTCGTCCCAACTCCCACCCACCGGCGTTTCTCCAGCTCG
ATCTGGAGGCTGCTTCGCCAGTGTGGGACGCAGCTGACGCCCGCTTATTAGCTCTCGCTGCGTCGCCCCGGCTC
AGAAGCTCCGTGGCGGCGGCGACCGTGACGAGAAGCCACGGCCAGCTCAGTTCTCTTCTACTTTGGGAGAGAG
AGAAAGTCAGATGCCCTTTTAAACTCCCTCTTCAAAACTCATCTCCTGGGTGACTGAGTTAATAGAGTGGATA
CAACCTTGCTGAAGATGAAGAATATACAATATTGAGGATATTTTTTCTTTTTTTTTTCAAGTCTTGATTTGTG
GCTTACCTCAAGTTACCATTTTTTCAGTCAAGTCTGTTTGTGCTTCTTCAGAAATGTTTTTTACAATCTCAAG
AAAAATATGTCCAGAAATTGAGTTTACTGTTGCTTGTATTTGGACTCATTGCGGGATTGATGTTACTGCACT
ATACTTTTCAACAACCAAGACATCAAAGCAGTGTCAAGTTACGTGAGCAAATACTAGACTTAAGCAAAGATAT
GTTAAAGCTCTAGCAGAGGAAAATAAGAACACAGTGGATGTCGAGAACGGTGCTTCTATGGCAGGATATGCGGA
TCTGAAAAGAACAATTGCTGTCCTTCTGGATGACATTTTGCAACGATTGGTGAAGCTGGAGAACAAGTTGACT
ATATTGTTGTGAATGGCTCAGCAGCCAACACCACCAATGGTACTAGTGGGAATTGGTGCCAGTAACCACAAAT
AAAAGAACAATGTCTCGGGCAGTATCAGATAGCAGTTGAAAATCACCTTGTGCTGCTCCATCCACTGTGGATT
ATATCCTATGGCAGAAAAGCTTTATAATTGCTGGCTTAGGACAGAGCAATACTTTACAATAAAAGCTCTACACA
TTTTCAAGGAGTATGCTGGATTCTAGGAACTCTAATTCTGTACATAAAAATTTTAAAGTTATTTGTTGCTTTC
AGGCAAGTCTGTTCAATGCTGTACTATGTCCTTAAAGAGAATTTGGTAACTTGGTTGATGTGGTAAGCAGATAG
GTGAGTTTGTATAAATCTTTTGTGTTGAGATCAAGCTGAAATGAAAACACTGAAAAACATGGATTCAATTTCT
ATAACACATTTATTTAAGTATATAACACGTTTTTTGGACAAGTGAAGAATGTTTAATCATTCTGTCAATTTGTTT
TCAATAGATGTAACCTGTTAGACTACGGCTATTTGAAAAATGTGCTTATTGTACTATATTTTGTATTCCAATT
ATGAGCAGAGAAAGGAAATATAATGTTGAAAATAATGTTTTGAAATCATGACCCAAAGAATGTATTGATTTGCA
CTATCCTTCAGAATAACTGAAGGTTAATTATTGTATATTTTAAAAATTACACTTATAAGAGTATAATCTTGAA
ATGGGTAGCAGCCACTGTCCATTACCTATCGTAAACATTGGGGCAATTTAATAACAGCATTAATAAGTTGTAA
ACTCTAATCTTATACCTTATTGAAGAATAAAAGATATTTTATGATGAGAGTAACAATAAAGTATTCTGATTTT
TCACATACATGAATGTTCAATTTAAAGTTTAATCCTTTGAGTGTCTATGCTATCAGGAAAGCACATTATTTCCA
TATTTGGGTAAATTTTGCTTTTATTATATTGGTCTAGGAGGAAGGGACTTTGGAGAATGGAACCTTGAGGACT
TTAGCCAGGTGTATATAATAAGGTACTTTTGTGCTGCATTAAATTGCTTGAAAGTGTTAACATTATATTATA
TAAGAGTATCCTTTATGAAATTTTGAATTTGTATAACAGATGCATTAGATATTCAATTTATATAATGGCCACTT
AAAAATAAGAACATTTAAATATAAACTATGAAGATTGACTATCTTTTCAGGAAAAAGCTGTATATAGCACAGG
GAACCCTAATCTTGGGTAATTCTAGTATAAAACAAATTATACTTTTATTTAAATTTCCCTTGTAGCAAATCTAA
TTGCCACATGGTGCCCTATATTTCATAGTATTTATCTCTATAGTAACTGCTTAAGTGCAGCTAGCTTCTAGAT
TTAGACTATATAGAATTTAGATATTGTATTGTTTCGTCAATATAATATGCTACCACATGTAGCAATAATTACAAT
ATTTTATTAATAATAATATGTGAAATATTGTTTCATGAAAGACAGATTTCCAAATCTCTCTCTCTCTCTGTA
CTGTCTACCTTTATGTGAAGAAATTAATTATATGCCATTGCCAGGT

FIGURE 70

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></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA77648
><subunit 1 of 1, 140 aa, 1 stop
><MW: 15668, pI: 10.14, NX(S/T): 5
MFFTISRKNMSQKLSLLLLVFGLIWGLMLLHYTFQQPRHQSSVKLREQILDLSKRYVKALA
EENKNTVDVENGASMAGYADLKRTIAVLLDDILQRLVKLENKVDYIVVNGSAANTTNGTSG
NLVPVTTNKRTNVSGSIR
```

Important features of the protein:

Signal peptide:

amino acids 1-26

FIGURE 71

GCTGAGCGTGTGCGCGGTACGGGGCTCTCCTGCCTTCTGGGCTCCAACGCAGCTCTGTGGCTGAACTGGGTGCT
CATCACGGGAAGTGTGGGCTATGGAATACAGATGTGGCAGCTCAGGTAGCCCCAAATGCCTGGAAGAATACA
TCATGTTTTTCGATAAGAAGAAATTGTAGGATCCAGTTTTTTTTTTAACCGCCCCCTCCCCACCCCCCAAAAAA
ACTGTAAAGATGCAAAAACGTAATATCCATGAAGATCCTATTACCTAGGAAGATTTTGATGTTTTGCTGCGAAT
GCGGTGTTGGGATTTATTTGTTCTTGGAGTGTCTGCGTGGCTGGCAAAGAATAATGTCCAAAATCGGTCCAT
CTCCAAGGGGTCCAATTTTCTTCTGGGTGTGAGCGAGCCCTGACTCACTACAGTGCAGCTGACAGGGGCTG
TCATGCAACTGGCCCCCTAAGCCAAAGCAAAGACCTAAGGACGACCTTTGAACAATACAAAGGATGGGTTTCAA
TGTAATTAGGCTACTGAGCGGATCAGCTGTAGCACTGGTTATAGCCCCCACTGTCTTACTGACAATGCTTTCTT
CTGCCGAACGAGGATGCCCTAAGGGCTGTAGGTGTGAAGGCAAAATGGTATATTGTGAATCTCAGAAATTACAG
GAGATACCTCAAGTATATCTGCTGGTTGCTTAGGTTTGTCCCTTCGCTATAACAGCCTTCAAAAACCTTAAGTA
TAATCAATTTAAAGGGCTCAACCAGCTCACCTGGCTATACCTTGACCATAACCATATCAGCAATATTGACGAAA
ATGCTTTTAAATGGAATACGCACTCAAGAGCTGATTCTTAGTTCCAATAGAATCTCCTATTTTCTTAACAAT
ACCTTCAGACCTGTGACAAATTTACGGAAGCTGGATCTGTCTCTATAATCAGCTGCATTCTCTGGGATCTGAACA
GTTTCGGGGCTTGCAGGAGCTGCTGAGTTTACATTTACGGTCTAACTCCCTGAGAACCATCCCTGTGCGAATAT
TCCAAGACTGCCGCAACCTGGAACCTTTGGACCTGGGATATAACCGGATCCGAAGTTTAGCCAGGAATGTCTTT
GCTGGCATGATCAGACTCAAAGAACTTCACCTGGAGCACAATCAATTTTCCAAGCTCAACCTGGCCCTTTTCC
AAGGTTGGTCAGCCTTCAGAACCTTTACTTGCAGTGAATAAAATCAGTGTCTATAGGACAGACCATGTCTGGG
CCTGGAGCTCCTTACAAAGGCTTGATTATCAGGCAATGAGATCGAAGCTTTCAGTGGACCCAGTGTTTTCCAG
TGTGTCCCAATCTGCAGCGCTCAACCTGGATTCCAACAAGCTCACATTTATTGGTCAAGAGATTTTGGATTCT
TTGGATATCCCTCAATGACATCAGTCTTGCTGGGAATATATGGGAATGCAGCAGAAATATTGCTCCCTTGTA
ACTGGCTGAAAAGTTTTAAAGGTCTAAGGGAGAATACAATTATCTGTGCCAGTCCCAAAGAGCTGCAAGGAGTA
AATGTGATCGATGCAGTGAAGAACTACAGCATCTGTGGCAAAGTACTACAGAGAGGTTTGATCTGGCCAGGGC
TCTCCCAAAGCCGACGTTTAAGCCCAAGCTCCCCAGGCCGAAGCATGAGAGCAAACCCCTTTGCCCCGACGG
TGGGAGCCACAGAGCCCGGCCAGAGACCGATGCTGACGCCGAGCACATCTTTCCATAAAATCATCGCGGGC
AGCGTGGCGCTTTTCTGTCCGTGCTCGTCATCTGCTGTTATCTACGTGTCTGGAAGCGGTACCTGCGAG
CATGAAGCAGCTGCAGCAGCGCTCCCTCATGCGAAGGCACAGGAAAAGAAAAGACAGTCCCTAAAGCAAATGA
CTCCCAGCACCCAGGAATTTTATGTAGATTATAAAACCCACCAACACGGAGACCAGCGAGATGCTGCTGAATGGG
ACGGGACCTGCACCTATAACAAATCGGGCTCCAGGGAGTGTGAGGTATGAACCATTTGTGATAAAAGAGCTCT
TAAAAGCTGGGAAATAAGTGGTGCTTTATTGAACTCTGGTGACTATCAAGGGAACGCGATGCCCCCTCCCT
TCCCTCTCCCTCTCACTTTGGTGGCAAGATCCTTCCTTGTCCGTTTTAGTGCATTATAATACTGGTCATTTTC
CTCTCATACATAATCAACCCATTGAAATTTAAATACCACAATCAATGTGAAGCTTGAACCCGGTTTTAATATA
TACCTATTGTATAAGACCTTTACTGATTCCATTAATGTGCGATTTGTTTTAAGATAAACTTCTTTTCATAGGT
AAAAAAAAAA

FIGURE 72

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA77301

><subunit 1 of 1, 513 aa, 1 stop

><MW: 58266, pI: 9.84, NX(S/T): 4

MGFNVIRLLSGSAVALVIAPTVLLTMLSSAERGCPKGCRCEGKMVYCESQKLQEIPSSISA
GCLGLSLRYNSLQKLKYNQFKGLNQLTWLYLDHNNHISNIDENAFNGIRRLKELILSSNRIS
YFLNNTFRPVTNLRNLDLSYNQLHSLGSEQFRGLRKLLSLHLRSNSLRTIPVRIFQDCRNL
ELLDLGYNRIRSLARNVVFAGMIRLKEHLHLEHNQFSKLNALFPRLVSLQONLYLQWNKISVI
GQTMSWTWSSLQRLDLGNEIEAFSGPSVFCVFNQLQRLNLDNKLTFIGQEILDSWISLN
DISLAGNIWECSRNICSLVNWLKSFKGLRENTIICASPKELQGVNVIDAVKNYSICGKSTT
ERFDLARALPKPTFKPKLPRPKHESKPPLPPTVGATEPGPETDADAEHISFHKIIAGSVAL
FLSVLVILLVIYVSWKRYPASMQLQQRSLMRRHRKKRQSLKQMTPTSTQEFYVDYKPTNT
ETSEMLLNGTGPTYNKSGSRECEV

Important features of the protein:

Signal peptide:

amino acids 1-33

Transmembrane domain:

amino acids 420-442

N-glycosylation sites.

amino acids 126-129, 357-360, 496-499, 504-507

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 465-468

Tyrosine kinase phosphorylation site.

amino acids 136-142

N-myristoylation sites.

amino acids 11-16, 33-38, 245-250, 332-337, 497-502, 507-512

FIGURE 73

CCAAGGCCAGAGCTGTGGACACCTTATCCCACTCATCCTCATCCTCTTCCTCTGATAAAGCCCCTACCAAGTGCT
GATAAAGTCTTTCTCGTGAGAGCCTAGAGGCCTTAAAAAAAAGTGCTTGAAAGAGAAGGGGACAAAGGAACA
CCAGTATTAAGAGGATTTTCCAGTGTTTCTGGCAGTTGGTCCAGAAGGATGCCTCCATTCCTGCTTCTCACCTG
CCTCTTCATCACAGGCACCTCCGTGTACCCGTGGCCCTAGATCCTTGTTCTGCTTACATCAGCCTGAATGAGC
CCTGGAGGAACACTGACCACCAGTTGGATGAGTCTCAAGGTCTCCTCTATGTGACAACCATGTGAATGGGGAG
TGGTACCACTTCACGGGCATGGCGGGAGATGCCATGCCTACCTTCTGCATACCAGAAAACCACTGTGGAACCCA
CGCACCTGTCTGGCTCAATGGCAGCCACCCCTAGAAAGGCGACGGCATTGTGCAACGCCAGGCTTGTGCCAGCT
TCAATGGGAAGTGTCTCTGGAACACCACGGTGGAAGTCAAGGCTTGCCCTGGAGGCTACTATGTGTATCGT
CTGACCAAGCCCAGCGTCTGCTTCCACGTCTACTGTGGTCATTTTTATGACATCTGCGACGAGGACTGCCATGG
CAGCTGCTCAGATACCAGCGAGTGACATGCGCTCCAGGAAGTGTGCTAGGCCCTGACAGGCAGACATGCTTTG
ATGAAAATGAATGTGAGCAAAACAACGGTGGCTGCAGTGAGATCTGTGTGAACCTCAAAAACCTCCTACCGCTGT
GAGTGTGGGGTTGGCCGTGTGCTAAGAAGTGATGGCAAGACTTGTGAAGACGTTGAAGGATGCCACAATAACAA
TGGTGGCTGCAGCCACTCTTGCCCTGGATCTGAGAAAGGCTACCAGTGTGAATGTCCCCGGGGCTGGTGTGT
CTGAGGATAACCACACTTGCCAAGTCCCTGTGTTGTGCAAATCAAATGCCATTGAAGTGAACATCCCCAGGGAG
CTGGTTGGTGGCCTGGAGCTCTTCCTGACCAACACCTCCTGCCGAGGAGTGTCCAACGGCACCCATGTCAACAT
CCTCTTCTCTCAAGACATGTGGTACAGTGGTTCGATGTGGTGAATGACAAGATTGTGGCCAGCAACCTCGTGA
CAGGTCTACCCAAGCAGACCCCGGGGAGCAGCGGGGACTTCATCATCCGAACCAGCAAGCTGCTGATCCCGGTG
ACCTGCGAGTTTCCACGCCTGTACACCATTCTGAAGGATACGTTCCCAACCTTCGAAACTCCCCACTGGAAAT
CATGAGCCGAAATCATGGGATCTTCCCATTCCTCTGGAGATCTTCAAGGACAATGAGTTTGAAGAGCCTTACC
GGGAAGCTCTGCCCACCTCAAGCTTCGTGACTCCCTCTACTTTGGCATTGAGCCCGTGGTGCACGTGAGCGGC
TTGGAAAGCTTGGTGGAGAGCTGCTTTGCCACCCCACTCCAGATCGACGAGGTCTGAAATACTACCTCAT
CCGGGATGGCTGTGTTTCAAGTACTCGGTAAAGCAGTACACATCCCGGGATCACCTAGCAAAGCACTTCCAGG
TCCCTGTCTTCAAGTTTGTGGGCAAAGACCACAAGGAAGTGTCTTCTGCACTGCCGGGTCTTGTCTGTGGAGTG
TTGGACGAGCGTTCCCGCTGTGCCCAGGGTTGCCACCGGCAATGCGTCGTGGGGCAGGAGGAGGAGGACTCAGC
CGGTCTACAGGGCCAGACGCTAACAGGCGGCCCGATCCGCATCGACTGGGAGGACTAGTTCGTAGCCATACCTC
GAGTCCCTGCATTGGACGGCTCTGCTCTTTGGAGCTTCTCCCCCACC GCCCTTAAGAACATCTGCCAACAGC
TGGGTTCAAGCTTCACTGTGAGTTCAAGTCCAGCACCACCTCACTCTGATTCTGGTCCATTCAAGTGGGCA
CAGGTACAGCACTGCTGAACAATGTGGCCTGGGTGGGGTTTCATCTTTCTAGGGTTGAAACTAAACTGTCCA
CCCAGAAAGCACTACCCCATTTCCCTCATTCTTTCTTCACTTAAATACCTCGTGTATGGTGCAATCAGAC
CACAAAATCAGAAGCTGGGTATAATATTTCAAGTTACAAACCTAGAAAAATTAACAGTTACTGAAATTATGA
CTTAAATACCCAATGACTCCTTAAATATGTAAATTATAGTTATACCTTGAAATTTCAATTCAAATGCAGACTAA
TTATAGGGAATTTGGAAGTGTATCAATAAAACAGTATATAATTTT

FIGURE 74

MPPFLLLTCLFITGTSVSPVALDPCSAYISLNEPWRNTDQHLDSESGPPLCDNHVNGEWYH
FTGMAGDAMPTFCIPENHCGTHAPVWLNGSHPLEGDGIVQRQACASFNGNCCLWNTTVEVK
ACPGGYVYRLTKPSVCFHVYCGHFYDIEDCHGSCSDTSECTCAPGTVLGPDRQTCFDE
NECEQNNGGCSEICVNLKNSYRCECGVGRVLRSDGKTCEDEVEGCHNNNGGCSSHSCLGSEKG
YQCECPRGLVLSNHTCQVPVLCKSNAIEVNIPRELVGGLLELFLTNTSCRGVSNQTHVNI
LFSLKTCGTVVDVNDKIVASNLTGLPKQTPGSSGDFIIRTSKLLIPVTCEFPRLYTISE
GYVPNLRNSPLEIMSRNHGIFPFTLEIFKDNEFEOPYREALPTLKLRLSLYFGIEPVVHVS
GLESLVESCFATPTSKIDEVLKYYLIRDGCVSDSVKQYTSRDHLAKHFQVPVFKFVGKDH
KEVFLHCRVLVCGVLDERSRCAQGCHRRMRRGAGGEDSAGLQGQTLTGGPIRIDWED

Important features of the protein:

Signal peptide:

amino acids 1-16

N-glycosylation sites.

amino acids 89-93, 116-120, 259-263, 291-295, 299-303

Tyrosine kinase phosphorylation sites.

amino acids 411-418, 443-451

N-myristoylation sites.

amino acids 226-232, 233-239, 240-246, 252-258, 296-302,
300-306, 522-528, 531-537

Aspartic acid and asparagine hydroxylation site.

amino acids 197-209

ZP domain proteins.

amino acids 431-457

Calcium-binding EGF-like proteins.

amino acids 191-212, 232-253

FIGURE 75

CGCCAAGCATGCAGTAAAGGCTGAAAATCTGGGTACAGCTGAGGAAGACCTCAGACATGGAGTCCAGGATGTG
GCCTGCGCTGCTGCTGTCCACCTCCTCCCTCTCTGGCCACTGCTGTTGCTGCCCCCTCCACCGCCTGCTCAGG
GCTCTTCATCCTCCCCCTCGAACCCACAGCCCCAGCCCCCGCCCCCGTGTGCCAGGGGAGGCCCCCTCGGCCCCA
CGTCATGTGTGCGTGTGGGAGCGAGCACCTCCACCAAGCCGATCTCCTCGGGTCCCAAGATCAGTCGGCAAGT
CCTGCCTGGCACTGCACCCCCAGCCACCCCATCAGGCTTTGAGGAGGGGCGCCCTCATCCCAATACCCCTGGG
CTATCGTGTGGGGTCCACCGTGTCTCGAGAGGATGGAGGGGACCCCAACTCTGCCAATCCCGGATTTCTGGAC
TATGGTTTTGCAGCCCCCTCATGGGCTCGAACCCACACCCCAACTCAGACTCCATGCGAGGTGATGGAGATGG
GCTTATCCTTGGAGAGGCACCTGCCACCTGCGGCCATTCTGTTCTGGGGGCGGTGGGGAAGGTGTGGACCCCC
AGCTCTATGTACAATTACCATCTCCATCATATTGTTCTCGTGGCCACTGGCATCATCTTCAAGTTCTGCTGG
GACCGCAGCCAGAAGCGACGCAGACCCCTCAGGGCAGCAAGGTGCCCTGAGGCAGGAGGAGAGCCAGCAGCCACT
GACAGACCTGTCCCCGGCTGGAGTCACTGTGCTGGGGGCTTCGGGGACTCACCTACCCCCACCCCTGACCATG
AGGAGCCCCGAGGGGGACCCCGCTGGGATGCCCCACCCCAAGGGGGCTCCAGCCTTCCAGTTGAACCGGTGA
GGGCAGGGGCAATGGGATGGGAGGGCAAAGAGGGAAGGCAACTTAGGTTCTCAGAGCTGGGGTGGGGGTGCCCT
CTGGATGGGTAGTGAGGAGGCAGGCGTGGCTCCACAGCCCCCTGGCCCTCCCAAGGGGGCTGGACCAGTCTCT
CTCTGGGAGGCACCCCTTCCTTCTCCAGTCTCTCAGGATCTGTGTCTATTCTCTGCTGCCATAACTCCAACT
CTGCCCTCTTTGGTTTTTTCTCATGCCACCTTGTTCTAAGACAACTCTGCCCTCTTAACCTTGATTCCCCCTCTT
TGTCTTGAACCTTCCCCCTTCTATTCTGGCCTACCCCTTGGTTCTCTGACTGTGCCCTTTCCCTCTTCTCTCAGGA
TTCCCCCTGGTGAATCTGTGATGCCCCCAATGTTGGGGTGCAGCCAAGCAGGAGGCCAAGGGGCCGGCAGACCCC
CCATCCCACTGAGGGTGGGGCAGCTGTGGGGAGCTGGGGCCACAGGGGCTCCTGGCTCCTGCCCTTGACACCC
ACCCGGAACACTCCCCAGCCCCACGGGCAATCCTATCTGCTCGCCCTCCTGCAGGTGGGGGCTCACATATCTG
TGACTTCGGGTCCCTGTCCCCACCCCTGTGCACTCACATGAAAGCCTTGCACTCACCTCCACCTTCACAGGC
CATTTGCACACGCTCCTGCACCCCTCTCCCCGTCCATACCGCTCCGCTCAGCTGACTCTCATGTTCTCTCGTCTC
ACATTTGCACTCTCTCCTTCCCACATTCTGTGCTCAGCTCACTCAGTGGTCAGCGTTTCTTGACACTTTACCT
CTCATGTGCGTTTCCCGGCTGATGTTGTGGTGGTGTGCGGCGTCTCACTCTCTCCCTCATGAACACCCACCC
ACCTCGTTTCCGCAGCCCCTGCGTGTCTGCTCCAGAGGTGGGTGGGAGGTGAGCTGGGGGCTCCTTGGGCCCTCA
TCGGTCATGGTCTCGTCCCATTCACACCATTTGTTTCTCTGTCTCCCCATCCTACTCCAAGGATGCCGGCATC
ACCCTGAGGGCTCCCCCTTGGGAATGGGGTAGTGAGGCCCCAGACTTCACCCCCAGCCACTGCTAAAATCTGT
TTTCTGACAGATGGGTTTTGGGGAGTCGCCTGCTGCACTACATGAGAAAGGACTCCCATTTGCCCTTCCCTTT
CTCCTACAGTCCCTTTTGTCTTGTCTGTCTGGCTGTCTGTGTGTGTGCCATTCTCTGGACTTCAGAGCCCCCT
GAGCCAGTCCCTCCCTTCCCAGCCTCCCTTTGGGCCTCCCTAACTCCACCTAGGCTGCCAGGGACCGGAGTCAGC
TGGTTCAAGGCATCGGGAGCTCTGCCTCCAAGTCTACCCCTCCCTTCCCGGACTCCCTCCTGTCCCCCTCCTTT
CCTCCCTCCTTCCCTCCACTCTCCTTCCCTTTTGCTTCCCTGCCCTTTCCCCCTCCTCAGGTTCTTCCCTCCTTC
TCACTGGTTTTTCCACCTTCCCTTCCCTTCTTCCCTGGCTCCTAGGCTGTGATATATATTTTGTATTATCT
CTTTCTTCTTCTTGTGGTGATCATCTTGAATTACTGTGGGATGTAAGTTTCAAATTTTCAAATAAAGCCTTTG
CAAGATAA

FIGURE 76

Signal peptide: Amino acids 1-33

Transmembrane domain: Amino acids 178-198

cAMP- and cGMP-dependent protein kinase phosphorylation site:
Amino acids 210-214

N-myristoylation sites: Amino acids 117-123; 154-160; 214-220

Cell attachment sequence: Amino acids 149-152

MESRMWPALLLSHLLPLWPLLLLPLPPPAQGSSSSSRTTPPAPARPPCARGGPSAPRHVCVWERAPPPSRSPRVF
RSRRQVLPGTAPPATPSGFEEGPPSSQYPWAIWGPVTSREDGGDPNSANPGFLDYGFAAPHGLATPHPNSDSM
RGDGDGLILGEAPATLRPFLFGGRGEGVDPQLYVTITISIIIVLVATGIIFKFCWDRSQKRRRPSGQQGALRQE
ESQQPLTDLSPAGVTVLGAFGDSPTPTPDHEEPRGGPRPGMPHPKGAPAFQLNR

FIGURE 77

GGCTGCGCCCAGGCCGGCGGGCCCAGCAGCTGCGAACC GCGCGCACCACTGTTTCCGCGCCCGGGGACTTC
CCCCGCGGGGCTCAGAAGTGTGGGGTCGGTCGCTTGGCTTCCCCTGGCGTCAGCGACCCAGGGTAACCTCCTCC
ACTGCTGCGTGCCGTGCAGGCTGCCTGTGTGAGAGCCACGTGTGCCGCGCTCTGGGCACAGCCTTGGAAGTC
AGGACCGCGACGGCAGCAGAGCAGAAACCTTACAGAAACATGAAGCCCTCAACCATCTGCTACTCAGTTATTCTG
GGGCTGACGGCGGCTTCTAGAACATCCAGGTGTTCTGCAGATGCGAGAACTCATCCTGTAGTCACCAGATGGAG
TCCCAAACAGCCAAGCAGATGTAAGGCCTGTGCTGTGGCTCTGAGGCCCTGAATACAGAAGGGTCACCTTTCTTA
GTGGCCAAAGAGCAGTTGTTGACATTGATGTCTAATTATTGAACACGACCAGTCATTTTACTGAGCTGCAGTGA
GGAAACACTGACCATAGAAGATCAAGCCAAATGAGGGATTGCAAATTTCTGATTCTTTTGAATTAGGATTCCA
GATGGGGGCTCATTTCTACAGCCCCAACATTCTATAGCCGTTATCACTGCCATCACCAGTCCACCAGCAT
CTTCTTGACAGATTCCACCCCTGCTCCCCAGAGACTTCTGCTTTGAAAGTGAGCAGAAAGGAAGCTCTCAGAAA
AATCTCTAGTGGTGGCTGCCGTGCTCCAGACAATCGGAATCCTGCCTTCACCACCATGGGCTGGCTTTTCTA
AAGGTTTTGTTGGCGGGAGTGAGTTTTCTCAGGATTTCTTTATCCTCTTGTGGATTTTTCATCAGTGGGAAAAC
AAGAGGACAGAAGCCAACTTTGTGATTATTTTGGCCGATGACATGGGGTGGGGTGACCTGGGAGCAAAGTGGG
CAGAAACAAAGGACACTGCCAACCTTGATAAGATGGCTTCGGAGGGAATGAGGTTTGTGGATTTCCATGCAGCT
GCCTCCACCTGCTCACCTCCCGGGCTTCTTGCTCACCGGCCGGCTTGGCCTTCGCAATGGAGTCACACGCAA
CTTTCAGTCACTTCTGTGGGAGGCTTCCGCTCAACGAGACCACCTTGGCAGAGGTGCTGCAGCAGGCGGGTT
ACGTCACTGGGATAATAGGCAAATGGCATCTTGGACACCACGGCTCTTATCACCCCAACTTCCGTGGTTTTGAT
TACTACTTTGGAATCCCATATAGCCATGATATGGGCTGTACTGATACTCCAGGCTACAACCACCTCCTTGTCC
AGCGTGTCCACAGGGTGATGGACCATCAAGGAACCTTCAAAGAGACTGTTACACTGACGTGGCCCTCCCTCTTT
ATGAAAACCTCAACATTGTGGAGCAGCCGGTGAACCTTGAGCAGCCTTGCCCAGAAGTATGCTGAGAAAGCAACC
CAGTTTCATCCAGCGTGCAAGCACAGCGGGAGGCCCTTCTGCTCTATGTGGCTCTGGCCCATGCACGTGCC
CTTACCTGTGACTCAGCTACCAGCAGCGCCACGGGGCAGAAGCCTGTATGGTGCAGGGCTCTGGGAGATGGACA
GTCTGGTGGGCCAGATCAAGGACAAAGTTGACCACAGTGAAGGAAAAACATTCTCTGGTTTACAGGAGAC
AATGGCCCGTGGGCTCAGAAGTGTGAGCTAGCGGGCAGTGTGGGTCCCTTCACTGGATTTTGGCAAACCTCGTCA
AGGGGGAAGTCCAGCCAAGCAGACGACCTGGGAAGGAGGGCACCGGGTCCCAGCACTGGCTTACTGGCCTGGCA
GAGTTCCAGTTAATGTCAACAGCACTGCCTTGTTAAGCGTGCTGGACATTTTCCAACCTGTGGTAGCCCTGGCC
CAGGCCAGCTTACCTCAAGGACGGCGCTTTGATGGTGTGGACGTCTCCGAGGTGCTCTTTGGCCGGTCACAGCC
TGGGCACAGGGTGCTGTTCCACCCCAACAGCGGGCAGCTGGAGAGTTTGGAGCCCTGCAGACTGTCCGCTGG
AGCGTTACAAGGCCTTCTACATTACCGGTGGAGCCAGGGCGTGTGATGGGAGCATGGTGCCTGAGCTGCAGCAT
AAGTTTTCTCTGATTTTCAACCTGGAAGACGATACCGCAGAAGCTGTGCCCTAGAAAGAGGTGGTGCAGGTA
CCAGGCTGTGCTGCCCAGGTGAGAAAGGTTCTTGACAGCTCCTCCAAGACATTGCCAACGACAACATCTCCA
GCGCAGATTACACTCAGGACCTTCAGTAACTCCCTGCTGTAATCCCTACCAAATTGCCTGCCGCTGTCAAGCC
GCATAACAGACCAATTTTATTCCACGAGGAGGAGTACCTGGAAATTAGGCAAGTTTGCTTCAAATTTCAATT
TTACCTCTTTACAAACACACGCTTTAGTTTAGTCTTGAGTTTAGTTTGGAGTTAGCCTTGCATATCCCTTC
TGTATCCTGTCCCCCTCCACGCCGACCCGAGAGCAGCTGAGCTGCGCTGGCTCTGGGCAGGGAGTGTGCCCTTA
ATGGGAAGCACACGGGCTTTGGAGTCAGGCACAGGTGCCAGCTCCAGCTTTTGAACCTGGGCAATTGTTTAACC
TAACCTGCAAGTTGATTTTGGGGTTAAATAAAGGCATACATGAAAATGCCTGGCAACTTTAAAAA

FIGURE 78

MGWLFLKVLLAGVSFSGFLYPLVDFCISGKTRGQKPNFVIIILADDMGWGDLGANWAETKDT
ANLDKMASEGMRFVDFHAAASTCSPSRASLLTGRLGLRNGVTRNFAVTSVGGLPLNETTLA
EVLQQAGYVTGIIIGKWHLGHHGSYHPNFRGFDYYFGIPYSHDMGCTDTPGYNHPPCPACPO
GDGPSRNLQRDCYTDVALPLYENLNIVEQPVNLSSLAQKYAEKATQFIQRASTSGRPFLLY
VALAHMHVPLPVTQLPAAPRGRSLYGAGLWEMDSLVGQIKDKVDHTVKENTFLWFTGDNGP
WAQKCELAGSVGPFTGFWQTRQGGSPAKQTTWEGGHRVPALAYWPGRVPVNVVTSTALLSVL
DIFPTVVALAQASLPQGRRFDGVDVSEVLFGRSQPGHRVLFHPNSGAAGEFGALQTVRLER
YKAFYITGGARACDGSMPPELQHKFPLIFNLEDDTAEAVPLERGGAEYQAVLPEVRKVLAD
VLQDIANDNISSADYTDQDPSVTPCCNPYQIACRCQAA

Important features of the protein:.

Signal peptide:

amino acids 1-16

Transmembrane domain:

amino acids 353-373

N-glycosylation sites.

amino acids 117-120, 215-218, 356-359, 397-500

N-myristoylation sites.

amino acids 12-17, 33-38, 52-57, 97-102, 101-106, 113-118, 158-163, 328-333, 388-393, 418-423, 435-440, 436-441

Amidation site.

amino acids 382-385

Sulfatases signature 2.

amino acids 129-138

FIGURE 79

CGCGGCCGGGCCCGCGGGGTGAGCGTGCCGAGGCGGGCTGTGGCGCAGGCTTCCAGCCCCACCATGCCGTGGCC
CCTGCTGCTGCTGCTGGCCGTGAGTGGGGCCAGACAACCCGGCCATGCTTCCCCGGGTGCCAATGCGAGGTGG
AGACCTTCGGCCTTTTCGACAGCTTCAGCCTGACTCGGGTGGATTGTAGCGGCCTGGGCCCCACATCATGCCG
GTGCCCATCCCTCTGGACACAGCCCACTTGACCTGTCTCCAACCGGTGGAGATGGTGAATGAGTCGGTGTT
GGCGGGGCCGGGTACACGACGTTGGCTGGCCTGGATCTCAGCCACAACCTGCTCACCAGCATCTCACCCTG
CCTTCTCCCCGCTTCGCTACCTGGAGTCGCTTGACCTCAGCCACAATGGCCTGACAGCCCTGCCAGCCGAGAGC
TTCACCAGCTCACCCTGAGCGACGTGAACCTTAGCCACAACCAGCTCCGGGAGGTCTCAGTGTCTGCCCTTAC
GACGCACAGTCAGGGCCGGGCACTACACGTGGACCTCTCCACAACCTCATTCACCGCCTCGTGCCCCACCCCA
CGAGGGCCGGCCTGCCTGCGCCACCATTAGAGCCTGAACCTGGCCTGGAACCGGCTCCATGCCGTGCCAAC
CTCCGAGACTTGCCCTGCGCTACCTGAGCCTGGATGGGAACCTCTAGCTGTCAATTGGTCCGGGTGCCCTTCG
GGGGCTGGGAGGCCCTACACACCTGTCTCTGGCCAGCCTGCAGAGGCTCCCTGAGCTGGCGCCAGTGGCTTCC
GTGAGCTACCGGGCCTGCAGGTCTGGACCTGTCTGGGAACCCCAAGCTTAACTGGGCAGGAGCTGAGGTGTTT
TCAGGCTGAGCTCCCTGCAGGAGCTGGACCTTTCGGGCACCAACCTGGTGCCCTGCCTGAGGCGCTGCTCCT
CCACCTCCCCGCACTGCAGAGCGTCAGCGTGGGCCAGGATGTGCGGTGCCGGCGCCTGGTGCGGGAGGGCACCT
ACCCCGGAGGCCTGGCTCCAGCCCCAAGGTGCCCTGCACTGCGTAGACACCCGGGAATCTGCTGCCAGGGGC
CCCACCATCTTGTGACCAAATGGTGTGGCCCAGGGCCACATAACAGACTGCTGTCTGGGCTGCCTCAGGTCCCG
AGTAACCTATGTTCAATGTGCCAACACCAAGTGGGGAGCCCGCAGGCCTATGTGGCAGCGTCACCACAGGAGTTG
TGGGCCTAGGAGAGGCTTTGGACCTGGGAGCCACACCTAGGAGCAAAGTCTCACCCCTTTGTCTACGTTGCTTC
CCCAAACCATGAGCAGAGGGACTTCGATGCCAAACCAAGACTCGGGTCCCCCTCCTGCTTCCCTTCCCCACTTATC
CCCCAAGTGCTTCCCTCATGCTGGGCGGGCCTGACCCGCAATGGGCAGAGGGTGGGTGGGACCCCCCTGCTGC
AGGGCAGAGTTCAGGTCCACTGGGCTGAGTGTCCCTTGGGCCCATGGCCCACTCACTCAGGGGCGAGTTTCTT
TTCTAACATAGCCCTTTCTTTGCCATGAGGCCATGAGGCCCGCTTCATCCTTTTCTATTTCCCTAGAACCTTAA
TGGTAGAAGGAATTGCAAAGAATCAAGTCCACCCCTTCTCATGTGACAGATGGGGAACTGAGGCCTTGAGAAGG
AAAAAGGCTAATCTAAGTTCTGCGGGCAGTGGCATGACTGGAGCACAGCCTCCTGCCTCCAGCCCCGACCCCA
ATGCACTTTCTTGTCTCCTCTAATAAGCCCCACCTCCCCGCCTGGGCTCCCTTGCTGCCCTTGCCCTGTTCCC
CATTAGCACAGGAGTAGCAGCAGCAGGACAGGCAAGAGCCTCACAAGTGGGACTCTGGGCCTCTGACCAGCTGT
GCGGCATGGGCTAAGTCACTCTGCCCTTCGGAGCCTCTGGAAGCTTAGGGCACATTGGTTCCAGCCTAGCCAGT
TTCTCACCCCTGGGTGGGGTCCCCAGCATCCAGACTGGAACCTACCCATTTTCCCTGAGCATCCTCTAGAT
GCTGCCCAAGGAGTTGCTGCAGTTCTGGAGCCTCATCTGGCTGGGATCTCCAAGGGGCTCCTGGATTGAGTC
CCCACTGGCCCTGAGCACGACAGCCCTTCTTACCCTCCAGGAATGCCGTGAAAGGAGACAAGGTCTGCCCGAC
CCATGTCTATGCTCTACCCCGAGGCGAGCATCTCAGCTTCCGAACCTGGGCTGTTTCTTAGTCTTCATTTTA
TAAAGTTGTTGCCCTTTTAAACGGAGTGTCACTTTCAACCGGCCTCCCTACCCCTGCTGGCCGGGGATGGAGA
CATGTCACTTTGTAAAAGCAGAAAAGGTTGCATTTGTTCACTTTTGTAATATTGTCTGGGCCTGTGTTGGGGT
GTTGGGGGAAGCTGGGCATCAGTGGCCACATGGGCATCAGGGGCTGGCCCCACAGAGACCCACAGGGCAGTGA
GCTCTGTCTTCCCCACCTGCCTAGCCCATCATCTATCTAACCGGTCTTGATTAAATAAACACTATAAAAGGT
TTAAAAA

FIGURE 80

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA77652

><subunit 1 of 1, 353 aa, 1 stop

><MW: 37847, pI: 6.80, NX(S/T): 2

MPWPLLLLLLAVSGAQTTRPCFPGCQCEVETFGLFDSFSLTRVDCSGLGPHIMPVPIPLDTA
HLDLSSNRLEMVNESVLAGPGYTTLAGLDLSHNLLTSISPTAFSRLRYLESLDLSHNGLTA
LPAESFTSSPLSDVNLSHNQLREVSVSFTTHSQGRALHVDLSHNLIHRLVPHPTRAGLPA
PTIQSLNLAWNRLHAVPNLRDLPLRYLSLDGNPLAVIGPGAFAGLGGLTHLSLASLQRLPE
LAPSGFRELPGLQVLDLSGNPKLNWAGAEVFSGLSLQELDLSGTNLVPLPEALLLHLPAL
QSVSVGQDVRCLRRLVREGTYPRRPGSSPKVPLHCVDTRESAARGPTIL

Signal peptide:

amino acids 1-16

Transmembrane domains:

amino acids 215-232, 287-304

FIGURE 81

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCACCCGTTAAGGTGTCTTCTCTTTAGGGATG
GTGAGGTTGGAAAAGACTCCTGTAACCCCTCCTCCAGGATGAACCACCTGCCAGAAGACAT
GGAGAACGCTCTCACCGGGAGCCAGAGCTCCCATGCTTCTCTGCGCAATATCCATTCCATC
AACCCACACAACCTCATGGCCAGGATTGAGTCCTATGAAGGAAGGGAAAAGAAAGGCATAT
CTGATGTCAGGAGGACTTTCTGTTTGTGTGTCACCTTTGACCTCTTATTCGTAACATTACT
GTGGATAATAGAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGAGGTGATG
CAGTATGACTACTATTCTTCATATTTTGATATATTTCTTCTGGCAGTTTTTTCGATTTAAAG
TGTTAATACTTGCATATGCTGTGTGCAGACTGCGCCATTGGTGGGCAATAGCGTTGACAAC
GGCAGTGACCAGTGCCTTTTTTACTAGCAAAAGTGATCCTTTCGAAGCTTTTCTCTCAAGGG
GCTTTTGGCTATGTGCTGCCCATCATTTTCATTCATCCTTGCCTGGATTGAGACGTGGTTCC
TGGATTTCAAAGTGTTACCTCAAGAAGCAGAAGAAGAAAACAGACTCCTGATAGTTCAGGA
TGCTTCAGAGAGGGCAGCACTTATACCTGGTGGTCTTTCTGATGGTCAGTTTTATTCCCCT
CCTGAATCCGAAGCAGGATCTGAAGAAGCTGAAGAAAACAGGACAGTGAGAAACCACTTT
TAGAACTATGAGTACTACTTTTGTAAATGTGAAAAACCCTCACAGAAAGTCATCGAGGCA
AAAAGAGGCAGGCAGTGGAGTCTCCCTGTGACAGTAAAGTTGAAATGGTGACGTCCACTG
CTGGCTTTATTGAACAGCTAATAAAGATTTATTTATTGTAATACCTCACAACGTTGTACC
ATATCCATGCACATTTAGTTGCCTGCCTGTGGCTGGTAAGGTAATGTCATGATTCATCCTC
TCTTCAGTGAGACTGAGCCTGATGTGTTAACAATAGGTGAAGAAAGTCTTGCTGTATT
CCTAATCAAAGACTTAATATATTGAAGTAACACTTTTTTTAGTAAGCAAGATACCTTTTTTA
TTTCAATTCACAGAATGGAATTTTTTTGTTTCATGTCTCAGATTTATTTTGTATTTCTTTT
TTAACTCTACATTTCCCTTGTTTTTTAACTCATGCACATGTGCTCTTTGTACAGTTTTTA
AAAAGTGAATAAAATCTGACATGTCAATGTGGCTAGTTTTATTTTTCTTGTTTTGCATTA
TGTGTATGGCCTGAAGTGTTGGACTTGCAAAAGGGGAAGAAAGGAATTGCGAATACATGTA
AAATGTCACCAGACATTTGTATTATTTTATCATGAAATCATGTTTTTCTCTGATTGTTCT
GAAATGTTCTAAATACTCTTATTTTGAATGCACAAAATGACTTAAACCATTATATCATGT
TTCCTTGCCTTCAGCCAATTTCAATTAAAATGAACTAAATTAAAAA

FIGURE 82

MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVTF
DLLFVTLLWIIELNVNGGIENLEKEVMQYDYYSSYFDIFLLAVFRFKVLILAYAVCRLRH
WWAIALTTAVTSAFLLAKVILSKLFSQGAFGYVLPPIISFILAWIETWFLDFKVLPPQEAEEE
NRLLIVQDASERAALIPGGLSDGQFYSPPESEAGSEEAEEKQDSEKPLLEL

Important features of the protein:

Signal peptide:

amino acids 1-20

Transmembrane domains:

amino acids 54-72, 100-118, 130-144, 146-166

N-myristoylation sites.

amino acids 14-20, 78-84, 79-85, 202-208, 217-223

FIGURE 83

CCGTCATCCCCCTGCAGCCACCCCTTCCCAGAGTCCTTTGCCAGGCCACCCAGGCTTCTT
GGCAGCCCTGCCGGGCCACTTGTCTTCATGTCTGCCAGGGGGAGGTGGGAAGGAGGTGGGA
GGAGGGCGTGCAGAGGCAGTCTGGGCTTGGCCAGAGCTCAGGGTGCTGAGCGTGTGACCAG
CAGTGAGCAGAGGCCGGCCATGGCCAGCCTGGGGCTGCTGCTCCTGCTCTTACTGACAGCA
CTGCCACCGCTGTGGTCCTCCTCACTGCCTGGGCTGGACACTGCTGAAAGTAAAGCCACCA
TTGCAGACCTGATCCTGTCTGCGCTGGAGAGAGCCACCGTCTTCCTAGAACAGAGGCTGCC
TGAAATCAACCTGGATGGCATGGTGGGGGTCCGAGTGCTGGAAGAGCAGCTAAAAAGTGTC
CGGGAGAAGTGGGGCCAGGAGCCCCCTGCTGCAGCCGCTGAGCCTGCGCGTGGGGATGCTGG
GGGAGAAGCTGGAGGCTGCCATCCAGAGATCCCTCCACTACCTCAAGCTGAGTGATCCCAA
GTACCTAAGAGAGTTCCAGCTGACCCTCCAGCCCCGGGTTTTTGAAGCTCCACATGCCTGG
ATCCCACTGATGCCTCCTTGGTGTACCCACGTTCCGGCCCCCAGGACTCATTCTCAGAGG
AGAGAAGTGACGTGTGCCTGGTGCAGCTGCTGGGAACCGGGACGGACAGCAGCGAGCCCTG
CGGCCTCTCAGACCTCTGCAGGAGCCTCATGACCAAGCCCGGCTGCTCAGGCTACTGCCTG
TCCCACCAACTGCTCTTCTCCTCTGGGCCAGAATGAGGGGATGCACACAGGGACCACTCC
AACAGAGCCAGGACTATATCAACCTCTTCTGCGCCAACATGATGGACTTGAACCGCAGAGC
TGAGGCCATCGGATACGCCCTACCCTACCCGGGACATCTTCATGAAAACATCATGTTCTGT
GGAATGGGCGGCTTCTCCGACTTCTACAAGCTCCGGTGGCTGGAGGCCATTCTCAGCTGGC
AGAAACAGCAGGAAGGATGCTTCGGGGAGCCTGATGCTGAAGATGAAGAATTATCTAAAGC
TATTCAATATCAGCAGCATTTTTTCGAGGAGAGTGAAGAGGCGAGAAAAACAATTTCCAGAT
TCTCGCTCTGTTGCTCAGGCTGGAGTACAGTGGCGCAATCTCGGCTCACTGCAACCTTTGC
CTCCTGGGTTCAAGCAATTCTCTTGCCTCATCCTCCCGAGTAGCTGGGACTACAGGAGCGT
GCCACCATACCTGGCTAATTTTTTATATTTTTTTAGTAGAGACAGGGTTTCATCATGTTGCT
CATGCTGGTCTCGAACTCCTGATCTCAAGAGATCCGCCCACCTCAGGCTCCCAAAGTGTGG
GATTATAGGTGTGAGCCACCGTGTCTGGCTGAAAAGCACTTTCAAAGAGACTGTGTTGAAT
AAAGGGCCAAGGTTCTTGCCACCCAGCACTCATGGGGGCTCTCTCCCCTAGATGGCTGCTC
CTCCCACAACACAGCCACAGCAGTGGCAGCCCTGGGTGGCTTCCTATACATCCTGGCAGAA
TACCCCCCAGCAAACAGAGAGCCACACCCATCCACACCGCCACCACCAAGCAGCCGCTGAG
ACGGACGGTTCCATGCCAGCTGCCTGGAGGAGGAACAGACCCCTTTAGTCCTCATCCCTTA
GATCCTGGAGGGCACGGATCACATCCTGGGAAGAAGGCATCTGGAGGATAAGCAAAGCCAC
CCCGACACCCAATCTTGAAGCCCTGAGTAGGCAGGGCCAGGGTAGGTGGGGGCCGGGAGG
GACCCAGGTGTGAACGGATGAATAAAGTTCAACTGCAACTGAAAAAAAAA

FIGURE 84

MSARGRWEGGGRRACRGSGLLARAQGAERVTSSEQRPAMASLGLLLLLLLLTALPPLWSSSL
PGLDTAESKATIADLILSALERATVFLEQRLPEINLDGMVGVRVLEEQLKSVREKWAQEPL
LQPLSLRVGMLGEKLEAAIQRSLSHYLKLSDPKYLREFQLTLQPGFWKLPHAWIHTDASLVY
PTFGPQDSFSEERSDVCLVQLLGTGTDSSSEPCGLSDLCRSLMTKPGCSGYCLSHQLLFFLW
ARMRGCTQGPLQQSQDYINLFCANMMDLNRRAEAIGYAYPTRDIFMENIMFCGMGGFSDFY
KLRWLEAILSWSQKQQEGCFGEFDAEDEELSKAIQYQQHFSRRVKRREKQFPDSRSVAQAGV
QWRNLGSLQPLPPGFKQFSLILPSSWDYRSVPPYLANFYIFLVETGFHHVAHAGLELLIS
RDPPTSGSQSVGL

Important features of the protein:

Signal peptide:

amino acids 1-26

Transmembrane domain:

amino acids 39-56

Tyrosine kinase phosphorylation sites.

amino acids 149-156, 274-282

N-myristoylation sites.

amino acids 10-16, 20-26, 63-69, 208-214

Amidation site.

amino acids 10-14

Glycoprotein hormones beta chain signature 1.

amino acids 230-237

FIGURE 85

GGTCTGAGTGCAGAGCTGCTGTCAATGGCGCCGCTCTGTGGGGCTTCTTTCCCGTCCTGCT
GCTGCTGCTGCTATCGGGGGATGTCCAGAGCTCGGAGGTGCCCGGGGCTGCTGCTGAGGGA
TCGGGAGGGAGTGGGGTCGGCATAGGAGATCGCTTCAAGATTGAGGGGCGTGCAGTTGTTC
CAGGGGTGAAGCCTCAGGACTGGATCTCGGCGGCCCGAGTGCTGGTAGACGGAGAAGAGCA
CGTCGGTTTTCTTAAGACAGATGGGAGTTTTGTGGTTCATGATATACCTTCTGGATCTTAT
GTAGTGGAAGTTGTATCTCCAGCTTACAGATTTGATCCCGTTCGAGTGGATATCACTTCGA
AAGGAAAAATGAGAGCAAGATATGTGAATTACATCAAAACATCAGAGGTTGTCAGACTGCC
CTATCCTCTCCAAATGAAATCTTCAGGTCCACCTTCTTACTTTATTAAAAGGGAATCGTGG
GGCTGGACAGACTTTCTAATGAACCCAATGGTTATGATGATGGTTCCTTCTTTATTGATAT
TTGTGCTTCTGCCTAAAGTGGTCAACACAAGTGATCCTGACATGAGACGGGAAATGGAGCA
GTCAATGAATATGCTGAATTCCAACCATGAGTTGCCTGATGTTTCTGAGTTCATGACAAGA
CTCTTCTCTTCAAAATCATCTGGCAAATCTAGCAGCGGCAGCAGTAAACAGGCAAAAGTG
GGGCTGGCAAAGGAGGTAGTCAGGCCGTCCAGAGCTGGCATTTCACAAACACGGCAACA
CTGGGTGGCATCCAAGTCTTGGAACCCTGTGAAGCAACTACTATAAACTTGAGTCATCC
CGACGTTGATCTCTTACAACCTGTGTATGTAACTTTTTTAGCACATGTTTTGTACTTGGTAC
ACGAGAAAACCCAGCTTTCATCTTTTGTCTGTATGAGGTCAATATTGATGTCACTGAATTA
ATTACAGTGTCTATAGAAAATGCCATTAATAAATTATATGAACTACTATACATTATGTAT
ATTAATTAAACATCTTAATCCAGAAATCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 86

MAAALWGFFPVLLLLLLSGDVQSSEVPGAAAEGSGGSGVGIGDRFKIEGRAVVPGVKPDW
ISAARVLVDGEEHVGFLKTDGSEFVVHDIPSGSYVVEVVSPAYRFDPRVDITSKGKMRARY
VNYIKTSEVVRLPYPLQMKSSGPPSYFIKRESWGWTDFLMNPMVMMMLVPLLLIFVLLPKVV
NTSDPDMRREMEQSMNMLNSNHELDPVSEFMTRLFSSKSSGKSSSGSSSKTGKSGAGKRR

Important features of the protein:

Signal sequence:

amino acids 1-23

Transmembrane domain:

amino acids 161-182

N-glycosylation site.

amino acids 184-187

Glycosaminoglycan attachment sites.

amino acids 37-40, 236-239

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 151-154

N-myristoylation sites.

amino acids 33-38, 36-41, 38-44, 229-234

Amidation site.

amino acids 238-241

ATP/GTP-binding site motif A (P-loop).

amino acids 229-236

[illegible]

FIGURE 88

MQGRVAGSCAPLGLLLVCLHLPGLFARSIGVVEEKVSNFGTNLPQLGQPSSTGPSNSEHP
QPALDPRSNDLARVPLKLSVPPSDGFPPAGGSAVQRWPPSWGLPAMDSWPPEDPWQMMAAA
AEDRLGEALPEELSYLSSAAALAPGSGPLPGESSPDATGLSPEASLLHQDSESRRRLPRSNS
LGAGGKILSQRPPWSLIHRVLPDHPWGTLNPSVSWGGGGPGTGWGTRPMPHPGEGIWGINNQ
PPGTSWGNIINRYPGGSWGNINRYPGGSWGNINRYPGGSWGNIHLYPGINNPFPFPGVLRPPG
SSWNIPAGFPNPPSPRLQWG

Important features of the protein:

Signal peptide:

amino acids 1-26

Casein kinase II phosphorylation sites.

amino acids 56-59, 155-158

N-myristoylation sites.

amino acids 48-53, 220-225, 221-226, 224-229, 247-252, 258-263,
259-264, 269-274, 270-275, 280-285, 281-286, 305-310

FIGURE 89

[illegible]

FIGURE 89 Continued

CCATTGCCTCAGTTGTGGTTCCCATTAATTATATGCCTCTCTATTATAATAGCATTCCCTATTCATCAATCAGAAG
AAACAGTGGATACCACTGCTTTGCTGGTATCGAACACCACTAAGCCTTCTTCCTTAAATAATCAGCTAGTATC
TGTGGACTGCAAGAAAGGAACCAGAGTCCAGGTGGACAGTTCCCAGAGAATGCTAAGAATTGCAGAACCAGATG
CAAGATTCAGTGGCTTCTACAGCATGCAAAAACAGAACCATCTACAGGCAGACAATTTCTACCAAACAGTGTGA
AGAAAGGCAACTAGGATGAGGTTTCAAAGACGGAAGACGACTAAATCTGCTCTAAAAGTAACTAGAATTG
TGCACTTGCTTAGTGGATTGTATTGGATTGTGACTTGATGTACAGCGCTAAGACCTTACTGGGATGGGCTCTGT
CTACAGCAATGTGCAGAACAAGCATTCCCACCTTTTCCTCAAAAAA

FIGURE 90

MYLVAGDRGLAGCGHLLVSLGLLLLLLARSSTRALVCLPCDESKCEEPRNCPGSIYQGVCGCCYTCASQRNESC
GGTFGIYGTCDRGLRCVIRPPLNGDSLTEYEAGVCEDENWTDQLLGFKPCNENLIAGCNIINGKCECNTIRTC
SNPFEPSPQDMCLSKRIEKEPDCSKARCEVQFSPRCPEDSVLIEGYAPPGECCPLPSRCVCNPAGCLRKVC
QPGNLLNLLVSKASGKPGECDDLYECKPVFGVDCRTVECPVQQTACPPDSYETQVRLTADGCCTLPTRCECLSG
LCGFPPVCEVGSTPRIVSRGDGTPGKCCDVFEVNDTKPACVFNNVEYYDGMFRMDNCRFCRCQGGVAICFTAQ
CGEINCERYVYVPEGECCPVCEDPVYFPNPNAGCYANGLILAHGDRWREDDCTFCQCVNGERHCVATVCGQTCTN
PVKVPGECCPVCEPTIITVDPPACGELSNCITLGKDCINGFKRDHNGCRTQCINTEELCSERKQGCTLNCPF
GFLTDAQNCEICECRPRPKCRPIICDKYCPLGLLKNKHGCDICRCKKCPELSCKICPLGFFQQDSHGCLCKC
REASASAGPPILSGTCLTVDGHKKNEESWHDGCRECYCLNGREMCALITCPVPACGNPTIHPGQCCPSCADDF
VVQKPELSTPSICHAPGGGEYFVEGETWNIDSCITQCTCHSGRVLCETEVCPPLLQCNPSRTQDSCCPQCTDQPF
PSLSRNNVSNYCKNDEGDIFLAESWKPVDCTSCICIDSVISCFSESCPSVSCERPVLKRGQCCPYCIEDTIP
KKVVCHFSGKAYADEERWDLDSCTHCYCLQGQTLCTSTVSCPLPCVEPINVEGSCCPMCPMYVPEPTNIPK
TNHREGEVDLEVPLWPTSENDIVHLPRDMGHLQVDYRDNRHLHPSSEDSSLDIASVVPVPIICLSIIIAFLFINQ
KKQWIPLLCWYRTPTKPSSLNNQLVSVDCCKGTRVQVDSSQRMRLIAEPDARFSGFYSMQKQNLQADNFYQTV

Important features of the protein:**Signal peptide:**

amino acids 1-34

Transmembrane domain:

amino acids 940-962

N-glycosylation sites.

amino acids 71-75, 113-117, 330-334, 474-478, 746-750

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 992-996

N-myristoylation site.

amino acids 9-15, 58-64, 61-67, 75-81, 79-85, 362-368, 402-408, 407-413,
439-445, 492-498, 511-517, 551-557, 558-564, 586-592,, 606-612, 625-631,
845-851

Prokaryotic membrane lipoprotein lipid attachment site.

amino acids 52-63, 844-855

Cell attachment sequence.

amino acids 314-317

Leucine zipper pattern.

amino acids 3-25

Eukaryotic thiol (cysteine) proteases cysteine active site.

amino acids 57-69

VWFC domain proteins.

amino acids 448-456, 382-390

C-terminal cystine knot proteins

amino acids 60-86

FIGURE 91

GCAAAAGGAAGGGAGGGAAGCACTCCATCATCTCACTGGGAAGAACGGCACGGGCATACCT
GCAGCTACTGGGGTTCCACTGGGCTTGAGGGTCGATTTTTTACCTTTTGAAGGACAAGATG
CATTGGAAGATGTTGCTGCTTCTGCTGTTGTATTACAATGCTGAGGCTTCTATGTGCCACA
GGTGGAGCAGGGCTGTGCTCTTCCCTGCCGCCACCGGCCAAAGAGGTCTCATCACTGCC
ATTGAACCCAGTCCTGCAGACCTCCCTGGAGGAGGTGGAGCTGCTCTACGAGTTCCTGCTG
GCCGAACCTTGAGATCAGCCCTGACCTGCAGATCTCCATCAAGGACGAGGAGCTGGCCTCCT
TGCGGAAGGCCTCAGACTTCCGCACCGTCTGCAACAACGTCATCCCCAAGAGCATCCCAGA
CATCCGCCGGCTCAGCGCCAGCCTCTCCAGCCACCCTGGCATCCTCAAGAAAGAAGACTTT
GAAAGGACAGTGCTGACCCTGGCCTACACAGCCTACCGCACAGCCCTGTCCACGGCCATC
AGAAGGACATCTGGGCGCAGTCCCTCGTTAGCCTCTTCCAGGCCCTGAGGCACGACTTGAT
GCGCTCCTCACAGCCGGGAGTACCTCCCTGAGAGACTGGCCACACCAGGACCTCAGAGCA
GGGACCAGCACAGTAATCCAGAAAGTCTTCATTCTCTACTCCATTTACAGAGACCAGCAAC
AAAACACTTACCGCTGACACAGAGCAGCAGAGATCAAACAGTAACCCCGATGCTCTTTTCT
CCTTGTAAGTTTCTGGAAGACACATCTGATTCATGCCATCATGTGACCTGGGCTGGAAGAA
AGGGCTGGAATGGTCATTCAAGACGCCTCCATGGGCAGAATGGTTTGCCTATGGCAGGCAG
AATTCTGATATGCTTCAACCCAGAGCAGTGGCCACACACTCAAGAGTGAGAACAGGCGTGA
GCCACCGTGCTGGCCCAGGATCTAAAACTTTCTAAGTTTCTCCTCATCGTTGGCATCCTC
ACAGCTATCTCCAATGTCACTCAAGAGACATCAACAGACATTTAACTGCTGCAGACTTCAT
TGCTCTGTACCTCACCTTGAATCTAACAAATCAAAGTATTTCTGCAGGTCCAATGGTCTA
AAATCAAATGCTTGTTAAATGACTTTTTTACAACACCCCTTACTTTTCTAATCCATTTCAAT
CTTATTTTTTTTTATTGTGGTAAAAACACATCACGTAAAATGTACCATCTTAACCATTTTT
AAGCATATGGTACAGCAGTGTTAACTCCATGCATGTTGTGAAACAGACCCCCGGAACTTTC
TCATCTTGTAATTCTGAAGTTCTATACCCACCGAACAACTCCTCTTTTCCCCTTCCCCCTG
CCTGCCCCAGCTCTTGGCACCATTTCTGCTTTCTGTTTTTGAGAGTCTGACTACTTAAG
ATACCTCATAACAAGCGGGATCTGGCTTACATTTCTTGAGCATTGTATTCTGGAAAAGTGTT
TCCTTCCTCTGAAAAATGGGTAGAGTTCTGAAGGAGAACTACTGGTCTTATTGTACACTTG
CTGTACCTATTTTTATTTAACAAATATTCATCTATGGTATAATAAAGATGTCATGGTTGGA
AAAAAAAAAAAAAAAAAAAAA

FIGURE 92

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA96893
><subunit 1 of 1, 173 aa, 1 stop
><MW: 19733, pI: 8.78, NX(S/T): 0
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LLAELEISPDQLQISIKDEELASLRKASDFRTVCNNVIPKSIPDIRRLSASLSSHPGILKK
EDFERTVLTLAYTAYRTALSHGHQKDIWAQSLVSLFQALRHDLMRSSQPGVPP

Important features of the protein:

Signal peptide:

Amino acids 1-17

cAMP- and cGMP-dependent protein kinase phosphorylation sites:

Amino acids 36-40;84-88;105-109.

FIGURE 93

CACCATGCTGGGGGTGCTCCCGGGGCCCCGCCGCGGGGACGGGCGTCTGCGGCTGGC
GCGACTAGCGCTGGTACTCCTGGGCTGGGTCTCCTCGTCTTCTCCACCTCCTCGGCATC
CTCCTTCTCCTCCTCGGCGCCGTTCTGGCTTCCGCCGTGTCCGCCAGCCCCGCTGCC
GGACCACTGCCCCGCGCTGTGCGAGTGTCCGAGGCAGCGCGCACAGTCAAGTGCCTTAA
CCGCAATCTGACCGAGGTGCCACGGACCTGCCCGCCTACGTGCGCAACCTCTTCTTAC
CGGCAACCAGCTGGCCGTGCTCCCTGCCGCGCCTTCGCCCCGCGGCCGCGCTGGCGGA
GCTGGCCGCGCTCAACCTCAGCGGCAGCCGCTGGACGAGGTGCGCGCGGGCGCCTTCGA
GCATCTGCCCAGCTGCGCCAGCTCGACCTCAGCCACAACCCACTGGCCGACCTCAGTCC
CTTCGCTTTCTCGGGCAGCAATGCCAGCGTCTCGGCCCCAGTCCCCCTGTGGAAGTAT
CCTGAACCACATCGTGCCCCCTGAAGATGAGCGGCAGAACCGAGCTTCGAGGGCATGGT
GGTGGCGGCCCTGCTGGCGGGCCGTGCACTGCAGGGGCTCCGCCGCTTGGAGCTGGCCAG
CAACCACTTCCTTTACCTGCCGCGGGATGTGCTGGCCCAACTGCCAGCCTCAGGCACCT
GGACTTAAGTAATAATTGCTGGTGAGCCTGACCTACGTGTCTTCCGCAACCTGACACA
TCTAGAAAGCCTCCACCTGGAGGACAATGCCCTCAAGGTCTTCACAATGGCACCCCTGGC
TGAGTTGCAAGGTCTACCCACATTAGGGTTTCTTGGACAACAATCCCTGGGTCTGCGA
CTGCCACATGGCAGACATGGTGACCTGGCTCAAGGAAACAGAGGTAGTGCAGGGCAAAGA
CCGGCTCACCTGTGCATATCCGGAAAAAATGAGGAATCGGGTCTTCTTGGAAGTCAACAG
TGCTGACCTGGACTGTGACCCGATTCTTCCCCCATCCCTGCAAACCTCTTATGTCTTCCT
GGGTATTGTTTTAGCCCTGATAGGCGCTATTTTCTCCTGGTTTTGTATTTGAACCGCAA
GGGGATAAAAAAGTGGATGCATAACATCAGAGATGCCTGCAGGGATCACATGGAAGGGTA
TCATTACAGATATGAAATCAATGCGGACCCAGATTAAACAAACCTCAGTTCTAACTCGGA
TGCTGAGAAATATTAGAGGACAGACCAAGGACAACCTCTGCATGAGATGTAG

FIGURE 94

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></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA336539
><subunit 1 of 1, 420 aa, 1 stop
><MW: 46032, pI: 6.76, NX(S/T): 8
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QCPALCECSEAARTVKCVNRNLTEVPTDLPAYVRNLFLTGNQLAVLPAGAFARRPPLAEL
AALNLSGSRLDEVRAFAFEHLPSLRQLDLSHNPLADLSPFAFSGSNASVSAPSPLVELIL
NHIVPPEDERQNRSFEGMVVAALLAGRALQGLRRLELASNHFLYLPRDVLAQLPSLRHLD
LSNNSLVSLTYVSFRNLTHLESLHLEDNALKVLHNGTLAELQGLPHIRVFLDNNPWVDCD
HMADMVTWLKETEVVQGDRLTCAYPEKMNRVLELNSADLDCDILPPSLQTSYVFLG
IVLALIGAIFLLVLYLNKGIKKWMHNIRDACRDHMEGYHYRYEINADPRLTNLSSNSDV
```

FIGURE 95

GGCTTCTACAGTCCACAACACCCACCAGCCCCAGGCCAGCAGAATGAGCCCAGTGAGTG
CCGGGGCTCCCAGTTTGGCTGTTGCTATGACAACGTGGCCACTGCAGCCGGTCCTCTTGG
GGAAGGCTGTGTGGGCCAGCCAGCCATGCCTACCCCGTGCGGTGCCCTGCTGCCAGTGC
CCATGGCTCTTGTGCAGACTGGGCTGCCCGCTGGTACTTCGTTGCCTCTGTGGGCCAATG
TAACCGCTTCTGGTATGGCGGCTGCCATGGCAATGCCAATAACTTTGCCTCGGAGCAAGA
GTGCATGAGCAGCTGCCAGGGATCTCTCCATGGGCCCCGTCGTCCCCAGCCTGGGGCTTC
TGGAAGGAGCACCCACACGGATGGTGGCGGCAGCAGTCTGCAGGCGAGCAGGAACCCAG
CCAGCACAGGACAGGGGCCGCGGTGCAGAGAAAGCCCTGGCCTTCTGGTGGTCTCTGGCG
GCAAGACCAACAGCCTGGGCCAGGGGAGGCCCCCACACCCAGGCCTTTGGAGAATGGCC
ATGGGGGAGGAGCTTGGGTCCAGGGCCCCCTGGACTGGGTGGAGATGCCGGATCACCAGC
GCCACCTTCCACAGCTCCTCCTACAGATCTCACTTCCACCTCTCCAGGATTAGCTTGG
CAGGTGTGGAGCCCTCGTTGGTGCAGGCAGCCCTGGGGCAGTTGGTGGGCTCTCCTGCT
CAGACGACACTGCCCCGAATCCCAGGCTGCCTGGCAGAAAGATGGCCAGCCCATCTCCT
CTGACAGGCACAGGCTGCAGTTCGACGGATCCCTGATCATCCACCCCTGCAGGCAGAGG
ACGCGGSCACCTACAGCTGTGGCAGCACCCGGCCAGGCCGCGACTCCAGAAGATCCAAC
TCCGCATTATAGGGGGTGACATGGCCGTGCTGTCTGAGGCTGAGCTGAGCCGCTTCCCTC
AGCCCAGGGACCCAGCTCAGGACTTTGGCCAAGCGGGGGCTGCTGGGCCCTGGGGCCA
TCCCCCTTTACACCCACAGCCTGCAAACAGGCTGCGTTTGGACCAGAACCAGCCCCGGG
TGGTGGATGCCAGTCCAGGCCAGCGGATCCGGATGACCTGCCGTGCCGAAGGCTTCCCGC
CCCCAGCCATCGAGTGGCAGAGAGATGGGCAGCCTGTCTCTTCTCCAGACACCAGCTGC
AGCCTGATGGCTCCCTGGTCATTAGCCGAGTGGCTGTAGAAGATGGCGGCTTCTACACCT
GTGTCGCTTTCAATGGGCAGGACCGAGACCAGCGATGGGTCCAGCTCAGAGTTCTGGGGG
AGCTGACAATCTCAGGACTGCCCCCTACTGTGACAGTGCCAGAGGGTGATACGGCCAGGC
TATTGTGTGTGGTAGCAGGAGAAAGTGTGAACATCAGGTGGTCCAGGAACGGGCTACCTG
TGCAGGCTGATGGCCACCGTGTCCACCAAGTCCCAGATGGCACGCTGCTCATTTACAACCT
TGCGGGCCAGGGATGAGGGCTCCTACATGTGCACTGCCTACCAGGGGAGCCAGGCAGTCA
GCCGCAGCACCCAGGTGAAGGTGGTCTCACCAGCACCCACCGCCAGCCAGGGACCCTG
GCAGGGACTGCGTCGACCAGCCAGAGCTGGCCAACCTGTGATTTGATCCTGCAGGCCAGC
TTTGTGGCAATGAGTATTACTCCAGCTTCTGCTGTGCCAGCTGTTCACGTTTCCAGCCTC
ACGCTCAGCCCATCTGGCAGTAGGGATGAAGGCTAGTTCCAGCCCCAGTCCAAAATAGTT
CATAGGGCTAGGGAGAAAGGAAGATGGACTCTTGGCTTCTCTCTCTGGCTGGCAAAGGG
AGTTATCTTCTGGAATACATTAGCTCTTTCAAAAACCCACCCAGTGTTTAGCCTCAACGG
CAGCCAGTTACCAGCTTCTCTCTGTAGCCTTCAGCAGTGTTTGCATCTCTGACATAACCA
CAGGCTGCTGTTTTCAAGAAGAGCAATCTGTTTGGATAAGAAAAACCTTTACTTTACAGC
TTCCCTTTATAATTTGTTACACAGGAATAGTTAAATGCATTTGTTTGTGTTTTTTGAG
ACGGAGTTTCACTCTTGTGTCAGGCTGGAGGGCAATGGCGCGATCTCAGCTCACTGCA
ACCTCCGCTCTCTGGGTCTTGATTCTCCTGTGTGAGCCTTCTGAGTAGCTGGGATTACA
GATGCCATATCACCATGCCCTGGGTAAATTTTGTATTTTGTAGTTGAGATGGGGTTTCGCCAT
GTTGGCCAGGCTGGTCTCGAACTTCTGACCTCAGATGATCTGCCCGCCTCAGCCTCCCAA
AGTGTGGGATTACAGGCATGAGCCACCACGCCAGCCATCAATGCATTTTTTTTATTTT
TTTTTTGAGACAGAGTTTCGCACTTCTTGGCCAGGCTGGAGTACAATGGTGGGATCTTGG
CTCACTGCAACCTCCACCTCCTGGGTTCAAGCGCTTCTCCAGCCTCAGCCTCCTGAGTAG

FIGURE 95 Continued

CTGGGATTACAGGTATGTGCCACCATGCCTGGCTAATTTTGTATTTTGGTGGAGACGGG
GTTTCTCCATGTTGGTCAGACTGGTCTTGAACTCCCGACCTCAGGTAATCCGCCCCGCCTC
CGCCTCCCAAAATGCTGGGATTAGAGGTGTGAGCCACTGTGCCCAGCCCATCAATGTGTT
TTAAAGCTAGCTGTCTAGGGTTCCACTTAATTTAAAGCTGGGCAGGAGATGTGTAATGAT
TTCAAAGTTAACACCTGTTTGTCTTCTAAAGGGCATGCCAAGTCCTGCTGTATCAGGGAA
GTATTCTGTGCTAAAATCAGCGATGGTTTCATTGCTCTAGTCTCTCTCACCCCTTCTAGGCA
GTGCATCAGTCAGCTCTAAATCTGGTGCAGAGGGTTAACAGCATAACCCCTGTTGGCAAA
ATGGAATAGATGTTAAGACCTCAAATAGGGATTTGGGATGAAACAGCTGCAGTTAGCACT
GTTATCTGAGCATGAAAGAAGTGGAAACGCTCCTTACGTCGAGATGTTGGACCTTGAAGC
CCTCCTGAGGCCAACATGCAAATCTGGCTGTGACGGTTCATCTGACACCTGTGTAAAGCT
GACCAGCCTGCTCTGTACAGTGACAATGAGGAGCCCCTCTCTTCTTAAAGTAGGAATCTG
TGAAACAAAATGTTTGTCTGCCAAAGACAAATCAGACTGTCAGTCATTAAAAACAGCATTA
GCAGGATGAGGATAGCAATGGGGAAGGGTTGTGGGCAATGCAGTAACAGGGAAATGGCTT
CAGAAATGGTTTGAGTTGGAAGACAACATTCTTCATCTCTCAGGACTTCTAATTCCTTGA
TGCTAAAAGAAGAGGCATGGATTCTATGAGCTTCCAAGTCCCTTTCCACTTTAACCTTCT
ACAAATCTTTTCAGAGGACTGCCTAGTAGCAAAGGTTATTCCTGGACACAGGAAAGACGGG
CATTACAGGGACCAAAGCTCTGAAAGGTGACTTTTATTACCAACACACTGGCTGGAAAAG
GGACAAACCACATCACGGGTGAGTGATACTTCTCAGTCTTCTCTACTCATTCAACAAAGG
AAATGTGGGCTGGGGCAGAGGTCTTTTTTTCATTTAATACTGGAAAAATATTGAAGAGCAT
CCATGTTCACTTATGGCTGGTTTGTCTATAGAAATTGGAAAAATAAGGCCACTTTTTTG

FIGURE 96

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><Thu Jun 24 12:35:18 PDT 1999 DNA62849 [min]
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA62849
><subunit 1 of 1, 477 aa, 1 stop
><MW: 51112, pI: 6.66, NX(S/T): 0
MGPVVPSLGLLEGAPTRMVAAVLQASRNPASTGQGPRCRES PGLLVVSGGKTNSLGQGR
PPTPRPLENGHGGRSLGPGPLDWVEMPDHQRHPSTAPPTDLTSHLSRISLAGVEPSLVQA
ALGQLVRLSCSDDTAPESQAAWQKDGPISDRHRLQFDGSLIIHPLQAEDAGTYSCGST
RPGRDSQKIQLRIIGGDMAVLSEAELSRFPQPRDPAQDFGQAGAAGPLGAIPSSHQPAN
RLRLDQNPQPRVVDASPGQIRIMTCRAEGFPPPAIEWQRDGPVSSPRHQLQPDGSLVISR
VAVEDGGFYTCVAFNGQDRDQRWVQLRVLGELTISGLPPTVTVPEDTARLLCVVAGESV
NIRWSRNLQPVQADGHRVHQSPDGTLLIYNLRARDEGSYMC SAYQGSQAVSRSTEVKVVS
PAPTAQPRDPGRDCVDQPELANCDLILQAQLCGNEYYS SFCCASC SRFQPHAQPIWQ
```

FIGURE 97

GGCGGCGGGAGCAGCGAAGGGGGCGGCAGGGATCCTCCAGGCTGCCGGCTGGGAAGGCGT
GGGCGACCCGGTGTGTGGCGCGCCAGAGCCCCGCGTTTCAGCCCTAGGGAAGGAAGCCA
GTTGAGGGAAGTTCTCCATGAATGTACGTCACAATGATGATGACCGACCAAATCCCTCTG
GAACTGCCACCATTGCTGAACGGAGAGGTAGCCATGATGCCCCACTTGGTGAATGGAGAT
GCAGCTCAGCATGTTATTCTCGTTCAAGTTAATCCAGGTGAGACTTTCACAATAAGAGCA
GAGGATGGAAACACTTCAGTGCAATCAAGGACCTGCTGAAGTTCCTCATGATGTCACCCAAT
GGATCCATTCTCTCCATTGATGTCCTCCAGGTATATCTCACAGGTGATTGAAGATAGT
ACTGGAGTCCGCGGGTGGTGGTCACACCCAGTCTCCTGAGTGTTATCCCCAAGCTAC
CCCTCAGCCATGTCTCAACCCATCATCTCCCTCCCTATCTGACTCACCATCCACATTTT
ATTCACTAATCAGACACGGCTTACTACCCACCTGTTACCGGACCTGGAGATATGCCGCCT
CAGTTTTTTCCCCAGCATCATCTTCCCCACACAATATATGGTGAGCAAGAAATTATACCA
TTTTATGGAATGTCAAGCTACATCACCCGAGAAGACCAGTACAGCAAGCCTCCGCACAAA
AAACTGAAAGACCGCCAGATCGATCGCCAGAACCGCCTCAACAGCCCTCCTTCTTCTATC
TACAAAAGCAGCTGCACAACAGTATACAATGGCTATGGGAAGGGCCATAGTGGTGGAAAGT
GGCGGAGGCGGCAGCGGTAGTGGTCCCGGAATTAAGAAAACAGAGCGACGAGCAAGAAGC
AGCCCAAAGTCGAATGATTGAGACTTGCAAGAATATGAGTTGGAAGTAAAGAGGGTGCAA
GACATTCCTTTCGGGAATAGAGAAACCACAGGTTTCTAATATTGAGGCAAGAGCAGTTGTG
TTGTCTCTGGGCTCCCCCTGTTGGACTTTCCTGTGGACCCACAGTGGTCTTTCCTTCCCC
TACAGTTACGAGGTGGCCTTATCAGACAAAGGACGAGATGGAAAATACAAGATAATTTAC
AGTGGAGAAGAATTAGAATGTAACCTGAAAGATCTTAGACCAGCAACAGATTATCATGTG
AGGGTGTATGCCATGTACAATCCGTAAAGGGATCCTGCTCCGAGCCTGTTAGCTTCACC
ACCCACAGCTGTGCACCCGAGTGTCTTTCCCCCTAAGCTGGCACATAGGAGCAAAAGT
TCACTAACCTTGCAAGTGAAGGCACCAATTGACAACGGTTCAAAAATCACCAACTACCTT
TTAGAGTGGGATGAGGGAAGAAAGAAATAGTGGTTTCAGACAGTGCTTCTTCGGGAGCCAG
AAGCACTGCAAGTTGACAAAGCTTTGTCCGGCAATGGGGTACACATTGAGGCTGGCCGCT
CGAAACGACATTGGCACCAGTGGTTATAGCCAAGAGGTGGTGTGCTACACATTAGGAAAT
ATCCCTCAGATGCCCTTCTGCACTAAGGCTGGTTCGAGCTGGCATCACATGGGTGACGTTG
CAGTGGAGTAAGCCAGAAGGCTGTTACCCGAGGAAGTGATCACCTACACCTTGGAATT
CAGGAGGATGAAAATGATAACCTTTCCACCCAAAATACACTGGAGAGGATTTAACCTGT
ACTGTGAAAAATCTCAAAAGAAGCACACAGTATAAATTCAGGCTGACTGCTTCTAATACG
GAAGGAAAAAGCTGTCCAAGCGAAGTCTTGTGTTGTACGACGAGTCTGACAGGCCTGGA
CCTCCTACCAGACCGCTTGTCAAAGGCCAGTTACATCTCATGGCTTTAGTGTCAAATGG
GATCCCCCTAAGGACAATGGTGGTTGAGAAATCCTCAAGTACTTGCTAGAGATTACTGAT
GGAAATTCTGAAGCGAATCAGTGGGAAGTGGCTACAGTGGGTGGCTACCGAATACACC
TTCACCCACTTGAAACCAGGCACCTTGTACAACTCCGAGCATGCTGCATCAGTACCGGC
GGACACAGCCAGTGTCTGAAAGTCTCCCTGTTGCGACACTAAGCATTGCACCAGGTCAA
TGTCGACCACCGAGGGTTTGGGTAGACCAAGCACAAAGAAGTCCACTTAGAGTGGGAT
GTTCTGTCATCGGAAAGTGGCTGTGAGGTCTCAGAGTACAGCGTGGAGATGACGGAGCCC
GAAGACGTAGCCTCGGAAGTGTACCATGGCCAGAGCTGGAGTGCACCGTCGGCAACCTG
CTTCCTGGAACCGTGTATCGCTTCCGGGTGAGGGCTCTGAATGATGGAGGGTATGGTCCC
TATTCTGATGTCTCAGAAATTACCACTGCTGCAGGGCCTCCTGGACAATGCAAAGCACCT
TGTATTTCTGTACACCTGATGGATGTGTCTTAGTGGGTTGGGAGAGTCTCTGATAGTTCT
GGTGCTGACATCTCAGAGTACAGGTGGAAATGGGGAGAAGATGAAGAATCCTTAGAACTC

FIGURE 97 Continued

ATTTATCATGGGACAGACACCCGTTTGTGAAATAAGAGACCTGTTGCCTGCTGCACAGTAT
TGCTGTAGACTACAGGCCTTCAATCAAGCAGGGGCAGGGCCGTACAGTGAACCTTGTCCTT
TGCCAGACGCCAGCGTCTGCCCCGTGACCCCGTCTCCACTCTCTGTGTCTGGAGGAGGAG
CCCCTTGATGCCTACCCGTGATTCACCTTCTGCGTGCCTTGTACTGAACTGGGAAGAGCCG
TGCAATAACGGATCTGAAATCCTTGCTTACACCATTGATCTAGGAGACACTAGCATTACC
GTGGGCAACACCACCATGCATGTTATGAAAGATCTCCTTCCAGAAACCACCTACCGGATC
AGAATTCAGGCTATAAATGAAATTGGAGCTGGACCATTTAGTCAGTTCATTAAAGCAAAA
ACTCGGCCATTACCACCCCTTGCCTCCTAGGCTAGAATGTGCTGCTGCTGGTCCCTCAGAGC
CTGAAGCTAAAATGGGGAGACAGTAACTCCAAGACACATGCTGCTGAGGACATTGTGTAC
ACACTACAGCTGGAGGACAGAAACAAGAGGTTTATTTCAATCTACAGAGGACCCAGCCAC
ACCTACAAGGTCCAGAGACTGACGGAATTCACATGCTACTCCTTCAGAATCCAGGCAGCA
AGCGAGGCTGGAGAAGGGCCCTTCTCAGAAACCTATACCTTCAGCACAACCAAAAGTGTC
CCCCCACCATCAAAGCACCTCGAGTAACACAGTTAGAAGTAAATTCATGTGAAATTTTA
TGGGAGACGGTACCATCAATGAAAGGTGACCCCTGTTAACTACATTCTGCAGGTATTGGTT
GGAAGAGAATCTGAGTACAAACAGGTGTACAAGGGAGAAGAAGCCACATTCCAAATCTCA
GGCCTCCAGACCAACACAGACTACAGGTTCCGCGTATGTGCGTGTGTCGCTGTTTAGAC
ACCTCTCAGGAGCTAAGCGGAGCCTTCAGCCCCCTCTGCGGCTTTTGTATTACAACGAAGT
GAGGTCTAGCTTACAGGGGACATGGGGAGCTTAGATGATCCCAAATGAAGAGCATGATG
CCTACTGATGAACAGTTTGCAGCCATCATTGTGCTTGGCTTTGCAACTTTGTCCATTTTA
TTTGCCCTTTATATTACAGTACTTCTTAATGAAGTAAACCCCAACAAAAGTAGAGGTATGAA
TTAATGCTACACATTTTAATACACACATTTATTAGATACTCCCTTTTAAAGCCCTTT
TGTTTTTTGATTTATATACTCTGTTTTACAGATTTAGCTAGAAAAAAATGTCAGTGTTT
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AAAAAAAAAAAAAAAAAAAA

FIGURE 98

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><MW: 132941, pI: 5.92, NX(S/T): 5
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HHLPPYLTHHPHFIHNSHTAYYPPVTGPGDMPPQFFPQHHLPHHTIYGEQEIIIPFYGMSSY
ITREDQYSKPPHKKLKDRQIDRQNRLNSPPSSYKSSCTTVYNGYKGHSGSGGGSGSGS
GPGIKKTERRARSSPKSNDSDLQEYELEVKRVQDILSGIEKPQVSNIQARAVVLSWAPPV
GLSCGPHSGLSFPYSYFVALSDKGRDGKYKIIYSGEELCNLKDRLPATDYHVRVYAMYN
SVKGCSEFPVSFTTHSCAPECPFPFKLAHRKSSLTQWKAPIDNGSKITNYLLEWDEGK
RNSGFRQCFFGSQKHCKLTKLCPAMGYTFRLAARNDIGTSGYSQEVVVCYTLGNIPQMPSA
LRLVRAGITWVTLQWSKPEGCSPEEVITYTLEIQEDENDNLFHPKYTGEDLTCTVKNLKR
STQYKFRLTASNTEGKSCPSEVLVCTTSPDRPGPPTRPLVKGPVTSHGFSVKWDPPKDNG
GSEILKYLLEITDGNSEANQWEVAYSGSATEYTFTHLKPGTLYKLRACCI STGGHSQCSE
SLPVRTL SIAPGQCRPPRVLGRPKHKEVHLEWDVPASESGCEVSEYSVEMTEPEDVASEV
YHGPELECTVGNLLPGTVYRFRVRALNDGGYGPYSDVSEITTAAGPPGQCKAPCISCTPD
GCVLVGWESPDSGGADISEYRLEWGEDEESLELIYHGTDTFRFEIRDLLPAAQYCCRLQAF
NQAGAGPYSELVLCQTPASAPDPVSTLCVLEEEPLDAYPDSPSACLVLNWEPCNNGSEI
LAYTIDLGDTSITVGNTTMHVMKDLLPETTYRIRIQAIN EIGAGPFSQFIKAKTRPLPPL
PPRLECAAAGPQSLKLKWDGSDNSKTHAAEDIVYTLQLEDNRNRFISYIRGPSHTYKVQRL
TEFTCYSFRIQAASEAGEGPFSEYTFSTTKSVPTTIKAPRVTQLEVNSCEILLWETVPSM
KGD PVNYILQVLVGRESEYKQVYKGEBA TFQISGLQTNTDYRFRVCACRRCLDTSQELSG
AFSPSAFVLQRSEVMLTGDMGSLDDPKMKSMMP TDEQFAAIIVLGFATLSILFAFILQY
FLMK
```

FIGURE 99

CCCAAAGAGGTGAGGAGCCGGCAGCGGGGGCGGCTGTAACCTGTGAGGAAGGCTGCAGAGTGGCGACGTCTACGC
CGTAGGTTGGAGGCTGTGGGGGTGGCCGGGCGCCAGCTCCCAGGCCGAGAAAGTGACCTGCGGTGGAGTCCC
TCCTCGCTGCTGGAGAACGGAGGGAGAAGGTTGCTGGCCGGGTGAAAGTGCCCTCCTCTGCTTGACGGGGCTGA
GGGGCCCGAAGTCTAGGGCGTCCGTAGTCGCCCCGGCCTCCGTGAAGCCCCAGGTCTAGAGATATGACCCGAGA
GTGCCCATCTCCGGCCCCGGGGCTGGGGCTCCGCTGAGTGGATCGGTGCTGGCAGAGCGGCAGTAGTGTGTTG
CAGTGGTGCTGAGCATCCACGCAACCGTATGGGACCGATACTCGTGGTGCGCCGTGGCCCTCGCAGTGCAGGCC
TTCTACGTCCAATACAAGTGGGACCGGCTGTACAGCAGGAAGCGCCGTCTTCCAGTTCCGAATGTCCGCAA
CAGTGGCCTATTGCCCGCTCCATGGTCATGCCCTTGCTTGGACTAGTCATGAAGGAGCGGTGCCAGACTGCTG
GGAACCCGTTCTTTGAGCGTTTGGCATTGTGGTGGCAGCCACTGGCATGGCAGTGGCCCTCTTCTCATCAGTG
TTGGGCTCGGCATCACTCGCCAGTGCCAACCAACACTTGTGTCTCTTGGGCTTGGCTGGAGGTGTTATCAT
TTATATCATGAAGCACTCGTTGAGCGTGGGGGAGGTGATCGAAGTCCTGGAAGTCCTTCTGATCTTCGTTTATC
TCAACATGATCCTGCTGTACCTGCTGCCCCGCTGCTTCACCCCTGGTGAGGCACTGCTGGTATTGGGTGGCATT
AGCTTTGTCTCTCAACCAGCTCATCAAGCGCTCTCTGACACTGGTGGAAAGTCAGGGGGACCCAGTGGACTTCTT
CCTGCTGGTGGTGGTAGTAGGATGGTACTCATGGGCATTTTCTTCAGCACTCTGTTTGTCTTCATGGACTCAG
GCACCTGGGCCTCCTCCATCTTCTTCACCTCATGACCTGTGTGCTGAGCCTTGGTGTGGTCTACCTGGCTG
CACCGGCTCATCCGAGGAATCCCCTGCTCTGGCTTCTTCAGTTTCTCTTCCAGACAGACACCCGCATCTACCT
CCTAGCCTATTGGTCTCTGCTGGCCACCTTGGCCTGCCTGGTGGTGTGTACCAGAATGCCAAGCGGTATCTT
CCGAGTCCAAGAAGCACCAGGCCCCCACCATCGCCCGAAAGTATTTCCACCTCATTGTGGTAGCCACCTACATC
CCAGGTATCATCTTTGACCGGCCACTGCTCTATGTAGCCGCCACTGTATGCCTGGCGGTCTTCATCTTCCTGGA
GTATGTGCGCTACTTCCGCATCAAGCCTTTGGGTCACTCTACGGAGCTTCTGTCCCTTTTCTGGATGAAC
GAGACAGTGGACCACTCATCTGACACACATCTACCTGCTCCTGGGCATGTCTCTTCCCATCTGGCTGATCCCC
AGACCTGACACAGAAAGGTAGCCTGGGAGGAGCCAGGGCCCTCGTCCCTATGCCGGTGTCTGGCTGTGGG
TGTGGGTGATACTGTGGCCTCCATCTTCGGTAGCACCATGGGGGAGATCCGCTGGCCTGGAACCAAAAAGACTT
TTGAGGGGACCATGACATCTATATTTGCGCAGATCATTTCTGTAGCTCTGATCTTAATCTTTGACAGTGGAGTG
GACCTAAACTACAGTTATGCTTGGATTTTGGGGTCCATCAGCACTGTGTCCCTCCTGGAAGCATACACTACACA
GATAGACAATCTCCTTCTGCCTCTCTACCTCCTGATATTGCTGATGGCCTAGCTGTTACAGTGCAGCAGCAGTG
ACGGAGGAAACAGACATGGGGAGGGTGAACAGTCCCCACAGCAGACAGCTACTTGGGCATGAAGAGCCAAGGTG
TGAAAAGCAGATTTGATTTTTCAGTTGATTTCAGATTTAAAATAAAAAGCAAAGCTCTCCTAGTTCTA

FIGURE 100

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><subunit 1 of 1, 538 aa, 1 stop

><MW: 59268, pI: 8.94, NX(S/T): 1

MTRECPSPAPGPGAPLSGSLAEAAVVFVAVLSIHATVWDRYSWCAVALAVQAFYVQYKW
DRLLQQGSAVFQFRMSANSGLLPASVMVPLLGLVMKERCQTAGNPFFERFGIVVAATGMA
VALFSSVLALGITRPVPTNTCVILGLAGGVIIYIMKHSLSVGEVIEVLEVLLIFVYLNMI
LLYLLPRCFTPGEALLVLGGISFVLNQLIKRSLTLVESQGDVPDFFLLVVVGMVLMGIF
FSTLFVFMDSGTWASSIFFHLMTCVLSLGVLPWLHRLIRRNPILLWLLQFLFQTDTRIYL
LAYWSLLATLACLVLVLYQNAKRSSSESKKHQAPTIARKYFHLIVVATYIPGIIFDRPLLY
VAATVCLAVFIFLEYVRYFRIKPLGHTLRSFLSLFLDERDSGPLILTHIYLLLGMSLPIW
LIPRPCTQKGS LGGARALVPYAGVLAVGVGDTVASIFGSTMGEIRWPGTKKTFEGTMTSI
FAQIISVALILIFDSGVLDNYSYAWILGSISTVSLLEAYTTQIDNLLLPLYLLILLMA

Important features of the protein:

Signal peptide:

Amino acids 1-36

Transmembrane domains:

Amino acids 77-95;111-133;161-184;225-248;
255-273;299-314;348-373;406-421;
435-456;480-497

N-glycosylation sites:

Amino acids 500-504

cAMP- and cGMP-dependent protein kinase phosphorylation site:

Amino acids 321-325

N-myristoylation sites:

Amino acids 13-19;18-24;80-86;111-117;
118-124;145-151;238-244;251-257;
430-436;433-439;448-454;458-464;
468-474;475-481;496-502;508-514

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 302-313

FIGURE 101

CACTGCCCGTCCGCTCTTCAGCAGCCGGTCGCGGGCGGTGGAAAAGCGAGTGAAGAGAGCGCGACGGCGGGCGGC
GGCGGGCGGCAGCTATTGCTGGACGGCCAGTGGGAGAGCGAGGCCTGAGCCTCTGCGTCTAGGATCAAAATGG
TTTCAATCCCAGAATACTATGAAGGCAAGAACGTCTCTCACAGGAGCTACCGGTTTTCTAGGGAAGGTGCTT
CTGGAAAAGTTGCTGAGGTCTTGTCTTAAGGTGAATTCAGTATATGTTTTGGTGAGGCAGAAAGCTGGACAGAC
ACCACAAGAGCGAGTGGAGAAGTCCTTAGTGGCAAGCTTTTTGACAGATTGAGAGATGAAAATCCAGATTTTA
GAGAGAAAATTATAGCAATCAACAGCGAACTCACCCAACCTAAACTGGCTCTCAGTGAAGAAGATAAAGAGGTG
ATCATAGATTCTACCAATATTATATTCCTACTGTGCAGCTACAGTAAGGTTTAATGAAAATTTAAGAGATGCTGT
TCAGTTAAATGTGATTGCAACGCGACAGCTTATTCTCTTGCAACAACAATGAAGAATCTGGAAGTGTTTCATGC
ATGTATCAACAGCATATGCCTACTGTAATCGCAAGCATATTGATGAAGTAGTCTATCCACCACCTGTGGATCCC
AAGAAGCTGATTGATTCTTTAGAGTGGATGGATGATGGCCTAGTAAATGATATCACGCCAAAATTGATAGGAGA
CAGACCTAATACATACATATACACAAAAGCATTGGCAGAATATGTTGTACAACAAGAAGGAGCAAACTAAATG
TGGCAATTGTAAGGCCATCGATTGTTGGTGCCAGTTGGAAAGAACCCTTTCCAGGATGGATTGATAACTTTAAT
GGACCAAGTGGTCTCTTTATTGCGGCAGGGAAAGGAATCTTCGAACAATACGTGCCTCCAACAATGCCCTTG
AGATCTTGTTCTGTAGATGTAGTTGTCAACATGAGTCTTGCGGCAGCCTGGTATTCGGAGTTAATAGACCAA
GAAACATCATGGTGTATAATTGTACAACAGGCAGCACTAATCCTTTCCACTGGGGTGAAGTTGAGTACCATGTA
ATTTCCACTTTCAAGAGGAATCCTCTCGAACAGGCCTTCAGACGGCCAATGTAAATCTAACCTCCAATCATCT
TTTATATCATTACTGGATTGCTGTAAGCCATAAGGCCCCAGCATTCTGTATGATATCTACCTCAGGATGACTG
GAAGAAGCCCAAGGATGATGAAAACAATAACTCGTCTTCACAAAGCTATGGTGTTCCTTGAATATTTACAAGT
AATTCTTGGGTTTGGAATACTGAGAATGTCAATATGTTAATGAATCACTAAACCTGAAGATAAAAAGACCTT
CAATATTGATGTACGGCAGTTACATTGGGCAGAATATATAGAGAACTACTGCTTGGGAACTAAGAAGTACGTAT
TGAATGAAGAAATGTCTGGCCTCCCTGCAGCCAGAAAACATCTGAACAAGTTGCGGAATATACGTTATGGTTTT
AATACTATCCTTGTGATCCTCATCTGGCGCATTTTTATTGCAAGATCACAAATGGCAAGAAATATCTGGTACTT
TGTGGTTAGTCTGTGTTACAAGTTTTTGTCTACTTCCGAGCATCCAGCACTATGAGATACTGAAGACCAAGGA
TTCAGCATTAGAACATCTATACATATGGTGATCTAAATGTACAAAATGTAAAATGTATAAGTCATCTCACTTTT
TGTCAAGACATTAAACCATCTTAGATCGGAGTGTGAAGTAAATTATGGTATATTTTATGTAACATTTTAATGTT
TATGCTCATAAAACCTTAGTGAACACACTGTGTTATGCCAGCTCAAATCTACAGTAGCCACCAAAACCATGACTT
AATATTTTGAGCCCTAGAAGAAAGGGGTGTGCTGAGGACAAGAGTGGGGAAATAGGAACACTGACCAGTATAAC
TGTGCAATTCTGGAACATATTAATTAATAATATGCCTTAACATATAGTGAATTTCTAATTTCTAATGTTTCAGT
GCAATGGAAGACATTTATTTGGACAGTATACTAGCAAAGTTGGTAGATATTTGATTCTTCATTTTTTGTTTTTT
TCATTAGTTGAAGTGGGTTTTAGTTTTGTTTAAATTTATAACCAGCGTATTTTCACATCATCTCTGAAGTTAAA
TGATATCAACATGAAAGAGATGTTCTCATTTTTCTTTTCTGATTAAACGTCTGATGCATATCATTTTTCTAT
AAGTAATCAGTTGCTTTTAAATCAGAAGGCTATATTATTCTAATGACCCCTATTCGATCTAAATGGGTTTGAGA
ATCCATATCAGCAACATACGTGTTTTTTGACAGAAAGTGAACAAATTCGGTAAACTGTTAGTATCAAAAAG
AATAGGAATACAGTTTTTCTTTTCCACATTATGATCAAATAAAAATCTGTGAGATTGTTAAAAA

FIGURE 102

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA94849

><subunit 1 of 1, 515 aa, 1 stop

><MW: 59357, pI: 9.40, NX(S/T): 3

MVSIPEYYEGKNVLLTGATGFLGKVLLEKLLRSCPKVNSVYVLVRQKAGQTPQERVEEVLS
GKLFDRDLRDENPDFREKIIAINSELTQPKLALSEEDKEVIIDSTNIIFHCAATVRFNENLR
DAVQLNVIATRQLILLAAQQMKNLVFMHVSTAYAYCNRKHIDEVVYPPFVDPKKLIDSLEW
MDDGLVNDITPKLIGDRPNTYIYTKALAEYVVOEGAKLNVAIVRPSIVGASWKEPFPGW
DNFNGPSGLFIAAGKGILRTIRASNNALADLVVDVVVNMSLAAWYSGVNRPRNIMVYNC
TTGSTNPFHWGEVEYHVISTFKRNPLEQAFFRRPNVNLTSNHLLYHYWIAVSHKAPAFLYDI
YLRMTGRSPRMMKTITRLHKAMVFLEYFTSNVWNTENVNMLMNQLNPEDKKTFFNIDVRQ
LHWAIEYIENYCLGTTKYVLNEEMSGLPARKHLNKLNRNIRYGFNTILVILIWRIFIARSQM
ARNIWFVVSLSYKFLSYFRASSTMR

Important features of the protein:

Transmembrane domain:

Amino acids 469-488

N-glycosylation sites:

Amino acids 283-287;304-308;341-345

Tyrosine kinase phosphorylation site:

Amino acids 160-169

N-myristoylation sites:

Amino acids 219-225;252-258;260-266;452-458

Leucine zipper pattern:

Amino acids 439-461

FIGURE 103

CCGGCGATGTCGCTCGTGCTGCTAAGCCTGGCCGCGCTGTGCAGGAGCGCCGTACCCCGAGAGCCGACCGTTCA
ATGTGGCTCTGAACTGGGCCATCTCCAGAGTGGATGCTACAACATGATCTAATCCCGGAGACTTGAGGGACC
TCCGAGTAGAACCTGTTACAAC TAGTGTGCAACAGGGGACTATTCAATTTTGATGAATGTAAGCTGGGTACTC
CGGGCAGATGCCAGCATCCGCTTGTGAAGGCCACCAAGATTGTGTGACGGGCAAAAGCAACTTCCAGTCTTA
CAGCTGTGTGAGGTGCAATTACACAGAGGCCCTTCCAGACTCAGACCAGACCCTCTGGTGGTAAATGGACATTTT
CCTACATCGGCTTCCCTGTAGAGCTGAACACAGTCTATTTTCATTGGGGGCCATAATATTCCTAATGCAATATG
AATGAAGATGGCCCTTCCATGTCTGTGAATTTACCTCACCAGGCTGCCTAGACCACATAATGAAATATAAAAA
AAAGTGTGTCAAGGCCGAAGCCTGTGGGATCCGAACATCACTGCTTGTAAAGAAGAATGAGGAGACAGTAGAAG
TGAAC TTCACAACCACTCCCCTGGGAAACAGATACATGGCTCTTATCCAACACAGCACTATCATCGGGTTTTCT
CAGGTGTTTGTAGCCACACCAGAAGAAACAAACGCGAGCTTCAGTGGTGATTCCAGTGACTGGGGATAGTGAAGG
TGCTACGGTGCAGCTGACTCCATATTTTCC TACTTGTGGCAGCGACTGCATCCGACATAAAGGAACAGTTGTGC
TCTGCCCAACAAACAGGCGTCCCTTTCCCTCTGGATAACAACAAAAGCAAGCCGGGAGGCTGGCTGCCTCTCCTC
CTGCTGTCTCTGCTGGTGGCCACATGGGTGCTGGTGGCAGGGATCTATCTAATGTGGAGGCACGAAAGGATCAA
GAAGACTTCCTTTTCTACCACCACACTACTGCCCCCATTAAGGTTCTTGTGGTTTACCCATCTGAAATATGTT
TCCATCACACAATTTGTTACTTCACTGAATTTCTTCAAACCATTCAGAGAAGTGAGGTATCCTTGAAAAGTGG
CAGAAAAAGAAAATAGCAGAGATGGGTCCAGTGCAGTGGCTTGCCACTCAAAGAAGGCAGCAGACAAAGTCGT
CTTCCTTCTTTCCAATGACGTCAACAGTGTGTGCGATGGTACCTGTGGCAAGAGCGAGGGCAGTCCCAGTGAGA
ACTCTCAAGACCTCTTCCCCCTTGCCCTTTAACCTTTTCTGCAGTGATCTAAGAAGCCAGATTATCTGCACAAA
TACGTGGTGGTCTACTTTAGAGAGATTGATACAAAAGACGATTACAATGCTCTCAGTGTCTGCCCCAAGTACCA
CCTCATGAAGGATGCCACTGCTTTCTGTGCAGAACTTCTCCATGTCAAGCAGCAGGTGTCAGCAGGAAAAAGAT
CACAGCCTGCCACGATGGCTGCTGCTCCTTGTAG

FIGURE 104

MSLVLLSLAALCRSAVPREPTVQCGSETGPSPEWMLQHDLPGLRDLRVEPVTTTSVATGDYSILMNVSWVLRA
DASIRLLKATKICVTGKSNFQSYSCVRCNYTEAFQTQTRPSGGKWTFSYIGFPVELNTVYFIGAHNIPNANMNE
DGPSMSYNFTSPGCLDHIMKYKKKCVKAGSLWDPNITACKNEETVEVNFNTTTPLGNNRYMALIQHSTIIGFSQV
FEPHQKKQTRASVVIPTGDSEGATVQLTPYFPTCGSDCIRHKGTVVLCPTGTGVPFPLDNNKSKPGGWLPLLLL
SLLVATWVLVAGIYLMWRHERIKKTSFSTTTLLPPIKVLVVYPSEICFHHTICYFTEFLQNHCRSEVILEKWQK
KKIAEMGPVQWLATQKKAADKVVFLLSNDVNSVCDGTCGKSEGPSSENSQDLFPLAFNLFCSDLRSQIHLHKYV
VVYFREIDTKDDYNALSVC PKYHLMKDATAFCAELLHV KQQVSAGKRSQACHDGCCSL

Signal sequence:

Amino acids 1-14

Transmembrane domain:

Amino acids 290-309

N-glycosylation sites:

Amino acids 67-70;103-106;156-159;
183-186;197-200;283-286

cAMP- and cGMP-dependent protein kinase phosphorylation sites:

Amino acids 228-231;319-322

N-myristoylation site:

Amino acids 116-121

Amidation site:

Amino acids 488-491

GCAGCTCACCCCTTCGCAAGCCGAGTGGGGGGAAGACAGACGCCCGCGCTTCGGGGTGGGACGCA
GGGGGCTCTCCGACCCGTGGGCAGACTCAGTGGGAGTGCAGACCCCGCACCACGGAGCGCC
ACATCGCCGTACACAAGCGGCTTGTGCTGGCCTTCGCTGTGTCCCTCGTGGCATTGCTCG
CGGTCACAATGCTCGCTGTGCTGCTCAGCCTGCGCTTCGACGAGTGCGGGGCGAGTGCCA
CGCCAGGCGCCGACGGTGGCCCCCTCAGGCTTTCCGGAGCGCGGCGGCAACGGGAGCCTCC
CTGGATCGGGCCCGCGCAACCACCACGCAAGGCGGGGACTCCTGGCAGCCCGAGGCGGGTG
GGGTGGCCAGTCCGGGGACCACGTGCGGCCAGCGCCGTTCGGAGGAGGAGCGGGAGCCGT
GGGAGCCGTGGACGCAGCTGCGCCTGTGCGGCCACCTGAAGCCGCTGCACCTACAATCTGT
TGCTCACCGCCTTCATGGAGAACTTCACTTCTCCGGGGAGGTCAACGTGGAGATCGCGT
GCCGGAACGCCACCCGCTACGTAGTGCTGCACGCTTCCCGAGTGGCGGTGGAGAAAAGTGC
AGCTGGCCGAGGACCGGGCGCTTCGGGGCTGTCCCTGTAGCCGGTTTTTTCTCTACCCGC
AAACCCAGGTCTTAGTGGTGGTGTGAATAGGACACTGGACGCGCAGAGGAATTACAATC
TGAAGATTATCTACAACGCGCTCATCGAGAATGAGCTCCTGGGCTTCTTCCGCAGCTCCT
ATGTGCTCCACGGGGAGAGAAGATTCTTGGTGTACTCAGTTTTCGCCTACACATGCCA
GAAAGGCATTTCTTGTTTTGATGAGCCAATCTACAAGGCTACTTTCAAAATCAGCATCA
AGCATCAAGCAACCTATTTATCTTTATCTAATATGCCAGTGGAACTTCCGTGTTTGAGG
AAGATGGATGGGTTACGGATCACTTTTCAGACCCCTCTCATGTCCACATATATTTAG
CCTGGGCAATTTGCAACTTCACATACAGAGAACTACCACCAAGAGTGGGGTGTAGTAC
GATTATATGCAAGACCTGATGCTATCAGAAGAGGATCCGGGGACTATGCTCTCCATATAA
CAAAGAGATTAAATAGAATTTTATGAAGACTACTTTAAAGTGCCCTATTCTTGCCAAAAC
TAGATCTTTTAGCTGTGCCTAAGCATCCGTATGCTGCTATGGAGAACTGGGGACTAAGTA
TTTTTGTGGAACAAAGAATACTGCTGGATCCCGAGTGTTCATCTATTTCTTATTTGCTGG
ATGTCACCATGGTCATTGTTCATGAGATATGTCACCAAGTGGTTTGGTGACCTTGTGACGC
CTGTGTGGTGGGAAGACGTGTGGCTGAAGGAAGGGTTTGCTCACTACTTTGAATTTGTTG
GTACAGACTACCTCTATCTGGCTGGAAACATGGAAGAGCAGAGGTTTCTGACCGATGTTT
TGCATGAAGTGATGCTGCTGGACGGTTTGGCCAGTTCCCATCCAGTATCACAGGAAGTGC
TGCAGGCAACAGATATTGACAGGGTGTGTTGACTGGATCGCATATAAAAGGGTGCTGCTT
TAATAAGAATGCTGGCTAATTTTATGGGCCATTGAGTTTTCCAGAGGGGTTTGCAAGATT
ATTTAACCATTCATAAGTATGGTAATGCAGCCAGAAATGATCTCTGGAATACATTATCGG
AGGCTTTAAAAAGAAATGGGAAATATGTAATATACAAGAAGTAATGGATCAGTGGACAC
TCCAGATGGGTTATCTGTTATCACCATCTTGGGAAACACAACAGCAGAAAAATAGAATAA
TAATTACCCAACAGCATTTTATCTATGATATCAGTGCTAAACTAAAGCACTTAAACTTC
AGAATAACAGTTACCTGTGGCAGATTCCATTAACTATTGTGGTAGGAAATAGAAGCCATG
TGCTTTCAGAAGCAATTATTTGGGTGTCTAACAAATCAGAGCACCACAGAATAACTTAT
TGGACAAAGGAAGCTGGCTGCTGGGGAACATCAATCAAAGTGGCTATTTTAGAGTCAACT
ATGACCTAAGGAACTGGAGATTATTAATTGATCAATTAATCCGAATCATGAGGTTCTTT
CTGTGAGTAACCGAGCGGGCTTGATCGATGATGCCTTCAGCCTAGCCAGGGCTGGCTATT
TGCCTCAGAAATATCTCTGGAGATTATCAGATACCTGTCTGAGGAGAAGGATTTTCTTC
CTTGGCATGCTGCCAGCCGAGCTCTTTATCCTCTAGATAAATTACTGGACCGCATGGAAA
ACTACAACATTTTCAATGAATATATTTTAAAGCAAGTTGCAACAACATATATCAAGCTTG
GGTGGCCGAAAAATAATTTTAAATGGATCTCTTGTTCAGCATCTTACCAACATGAAGAAC
TACGTAGAGAAGTTATAATGCTGGCCTGCAGTTTTTGGCAACAAGCACTGTACCAACAGG
CATCAACACTTATTTTCAAGATTGGATTTCCAGCAACAGGAACAGAATACCCTAAATGTTT

FIGURE 105 Continued

GAGACATCGTATACTGTACAGGAGTGTCACTACTGGATGAGGATGTCTGGGAATTCATAT
GGATGAAATTCATTCCACCACAGCAGTTTCTGAGAAGAAAATATTATTGGAAGCCTTAA
CTTGCACTGATGACAGGAATTTATTAAACAGGCTTCTAAATCTGTCACTGAATTCAGG
TGGTGCTGGATCAAGATGCAATTGATGTCTAATCCATGTAGCTCGAAATCCACATGGTC
GAGACCTTGCCCTGGAAGTTTTTCAGGGATAAATGGAAGATATTAAATACCAGGTATGGAG
AAGCATTTGTTTATGTATTCCAACTCATCAGTGGTGTACAGAATTTCTTAATACTGAAG
GTGAACTCAAAGAGCTCAAGAACTTCATGAAAACTATGATGGGGTAGCTGCTGCTTCTT
TCTCACGAGCTGTGGAAGCTGTGCAAGCCAATGTGCGCTGGAAAATGCTTTACCAAGACG
AGCTTTTCCAATGGTTAGGAAAAGCTCTAAGACACTAATATATGTATCTTATAAACAAAC
AATTCAACTCAGAAGTTTATGAGAAGACACGCTTTTTGTGGAATGAGGAAAATGTACTAC
CTAGAAAATGGCCAGATTTTCAGTGTAACTGTGGGAGGAATTTTTTTTTTTAGTTTTT
ATTTTTTGTTTTTGGGGGATATTTTTTATTTGTTTCATTCTGTTCTGTTTCTCTAC
TGGGTGTTCTCTCTAAAGAACTCTTGCAAGTGAACTAGCCATGATTGCTTCAGCTGT
ACATTCCTTGCTGTACAGGACCAAATATGATAGTGTGATGCTGTTGATGTTACAGTCAATT
TGGAAAAACATATTCAGAATATCTGTGCATGGATATATTGTCCTGCCTGTGTTCCAGCAT
GCTTATTTCAAACGTCCAGTGTGTGTGTGAATATGTGTTACACCTAGGATGGGCATTAT
GCAAAAGCACAAAGATTATATATGACAATCAGTATTGCAATGAAAGAAAACTAAAAACA
GAAATGATATTCTCAATTTTGGGCAATGTGAGAGGTAAAAAGCCCTTGACATGATGAAC
ATCACTTATTTCACTCTTGGATTGTCTGGCAATGATTACTGTGTTGCTAACTCATTTTC
TTTGAGTTAAAGCTGTGTATACATTTTAAAAGGCATATAGATAGTGTATGCATATGTATA
TGTACATAGGGAAGCCCCATATGTATATAGTATGTTGTACACTGCACATGTACAAAGAAT
GTCTTCAGATCAAAGAAAATTTATCTCTTTTATAAACTTAAGGACAGTTGCAAAAGGCT
TCAAGGAATTTATCTCAACATTATTCTTTCTATGTCCTAACTAAATTTCTCACTGTTAT
GAATTTTTCTACTTCTTGAACAGTGGTCTATTCTGCTACATGAAGATGAATACAAAC
AAAAATTTTGTATAAACTCCCAAAAAAAAAAAAAAAAAA

FIGURE 106

MGEDDAALRAGSRGLSDPWADSVGVRPRTTERHIAVHKRLVLAFAVSLVALLAVTMLAVL
 LSLRFDECGASATPGADGGPSGFPERGGNGSLPGSARRNHAGGDSWQPEAGGVASPGTT
 SAQPPSEEREPEWEPWTQLRLSGHLKPLHYNMLTAFMENFTFSGEVNVEIACRNATRYV
 VLHASRVAVEKVQLAEDRAFGAVPVAGFFLYPQTQVLVVVLNRTLDAQRNYNLKIITYNAL
 IENELLGFFRSSYVLHGERRFLGVTQFSPTHARKAFPCFDEPIYKATFKISIKHQATYLS
 LSNMPVETSVFEEDGWVTDHFSQTPLMSTYYLAWAICNFTYRETTTKSGVVVRLYARPD
 IRRSGDYALHITKRLIEFYEDYFKVPYSLPKLDLLAVPKHPYAAMENWGLSIFVEQRIL
 LDPSVSSISYLLDVTMIVVHEICHQWFGDLVTPVWVEDVWLKEGFAHYFEFVGTDYLYPG
 WNMBKQRFLTDVLHEVMLLDGLASSHPVSQEVQLATDIDRVFDWIAKKGAALIRMLANF
 MGHSVFQRLQDYLTIHKYGNAARNDLWNTLSEALKRNGKYVNIQEVMDQWTLQMGYPVI
 TILGNTTAENRIITQQHFIYDISAKTKALKLQNNSYLWQIPLTIVGNRSHVSSEAIIW
 VSNKSEHHRITYLDKGSWLLGNINQTYFRVNYDLRNWRLIDQLIRNHEVLSVSNRAGL
 IDDAFSLARAGYLPQNIPLIIRYLSEEKDFLPWHAASRALYPLDKLLDRMENYNIFNEY
 ILKQVATTYIKLGWPKNNFNGLSVQASYQHEELRREVIMLACSGNKHCHQQASTLISDW
 ISSNRNRIPLNVRDIVYCTGVSLLEDVWEFIWMKFHSTTAVSEKKILLEALTCSDDRNL
 LNRLNLNLSLNEVVLDQDAIDVIIHVARNPGRDLAWKFFRDKWKILNTRYGEALFMYSK
 LISGVTEFLNTEGELKELKNFMKNYDGVAAASFSRAVETVEANVRWKMLYQDELFWLQGLK
 ALRH

89-92 N-glycosylation site

160-163	N-glycosylation site
175-178	N-glycosylation site
222-225	N-glycosylation site
338-341	N-glycosylation site
605-608	N-glycosylation site
634-637	N-glycosylation site
649-652	N-glycosylation site
663-666	N-glycosylation site
684-687	N-glycosylation site
800-803	N-glycosylation site
906-909	N-glycosylation site
362-365	cAMP- and cGMP-dependent protein kinase phosphorylation site
126-129	Casein kinase II phosphorylation site
309-319	Casein kinase II phosphorylation site
340-343	Casein kinase II phosphorylation site
516-519	Casein kinase II phosphorylation site
570-573	Casein kinase II phosphorylation site
606-609	Casein kinase II phosphorylation site
671-674	Casein kinase II phosphorylation site
862-865	Casein kinase II phosphorylation site
893-896	Casein kinase II phosphorylation site
971-974	Casein kinase II phosphorylation site

FIGURE 106 Continued

520-527	Tyrosine kinase phosphorylation site
78-83	N-myristoylation site
87-92	N-myristoylation site
90-95	N-myristoylation site
118-123	N-myristoylation site
501-506	N-myristoylation site
604-609	N-myristoylation site
825-830	N-myristoylation site
987-992	N-myristoylation site
437-446	Neutral zinc metalloproteinases, zinc-binding region signature

FIGURE 107

CTTTCCTTATCTGTGTGTA CTCTTATCTCACTGTTCTATTTTTCTCCTCATTATATTA
ACTCTTTCTTACCTTTTTTTCTGAACTTCTAGGCCTTCTCTTTCCAGAACTGGTGGAAGA
CAAATGAAACGGCCAAGATGGTAAGAAACAAGCCGCATTTCTCCTTGGGGAGACTGATAA
TTTAAAAGGTTTGTGTGTGTCAGAAACATTCCCAGCTTCATCACCAACCCTTTCCTTCCAC
CTCTGCCCACTGGAGACCACTTACATCCCGAAGCGGACGCGGCAGCTGAAGTCAGGAAAC
CATGCATCACATTAGCAGGAGCCAACTGCAGACTTTAAACTCCGTTCAACATGTGGATGC
GGCAGAGAAATGACCTGTCCAGACAAGCCGGGGCAGCTCATAACTGGTTTCATCTGCTCC
CTGTGCGTCCCGCGGGTGCCTAAGCTCTGGAGCAGCCGGCGTCCAAGGACCCGGAGAAAC
CTTCTGCTGGGCATGCGTGTGCCATCTACTTGGGCTTCTGTTGAGCCAGGTGGGGAGG
GCCTCTCTCCAGCATGGACAGGCGGTGAGAAGGGGCCACATCGCAGCCGCGACACCGCC
GAGCCATCCTTCCCTGAGATACCCCTGGATGGTACCCTGGCCCTCCAGAGTCCAGGGC
AATGGGTCCACTCTGCAGCCCAATGTGGTGTACATTACCCTACGCTCCAAGCGCAGCAAG
CCGGCCAATATCCGTGGCACCGTGAAGCCCAAGCGCAGGAAAAAGCATGCAGTGGCATCG
GCTGCCCCAGGGCAGGAGGCTTTGGTCGGACCATCCCTTCAGCCGCAGGAAGCGGCAAGG
GAAGCTGATGCTGTAGCACCTGGGTACGCTCAGGGAGCAAACCTGGTTAAGATTGGAGAG
CGACCCTGGAGGTTGGTGCGGGGTCCGGGAGTGCAGCCGGGGGCCAGACTTCCTGCAG
CCCAGCTCCAGGGAGAGCAACATTAGGATCTACAGCGAGAGCGCCCCCTCCTGGCTGAGC
AAAGATGACATCCGAAGAATGCGACTCTTGGCGGACAGCGCAGTGGCAGGGCTCCGGCCT
GTGTCTCTAGGAGCGGAGCCCGTTTGTCTGGTGTCTGGAGGGGGCGCACCTGGCGCTGTG
CTCCGCTGTGGCCCTAGCCCCTGTGGGCTTCTCAAGCAGCCCTTGACATGAGTGAGGTG
TTTGCTTCCACCTAGACAGGATCCTGGGGCTCAACAGGACCTGCCGCTGTGTAGCAGG
AAAGCAGAGTTCATCCAAGATGGCCGCCCATGCCCCATCATTCCTTTGGGATGCATCTTTA
TCTTCAGCAAGTAATGACACCCATTCTTCTGTTAAGCTCACCTGGGGAACCTATCAGCAG
TTGCTGAAAAGAAATGCTGGCAGAAATGGCCGAGTACCCAAGCCTGAATCAGGTTGTACT
GAAATACATCATCATGAGTGGTCCAAGATGGCACTCTTTGATTTTTTTGTTACAGATTTAT
AATCGCTTAGATACAAATTGCTGTGGATTGAGACCTCGCAAGGAAGATGCCTGTGTACAG
AATGGATTGAGGCCAAAATGTGATGACCAAGGTTCTGCGGCTCTAGCACACATTATCCAG
CGAAAGCATGACCCAAGGCATTTGGTTTTTATAGACAACAAGGTTTCTTTGACAGGAGT
GAAGATAACTTAACTTCAAATGTGTTAGAAGGCATCAAAGAGTTTCCAGCTTCTGCAGTT
TCTGTTTGAAGAGCCAGCACTTACGGCAGAACTTCTTCAGTCTCTGTTTCTTGATAAA
GTGTATTGGGAAAGTCAAGGAGGTAGACAAGGAATTGAAAAGCTTATCGATGTAATAGAA
CACAGAGCCAAAATCTTATCACCTATATCAATGCACACGGGGTCAAAGTATTACCTATG
AATGAATGACAAAAGAATCTTCTGGCTAGGGTGTAGATATATTTATGCATTTTTGGTTT
TGTTTTTAAATCAAGCACATCAACCTCAAGCCCGTTTAGCAATGAGGCAGTGTAGATGAA
TACGTAAAATAAATGACTTTAACCAGTAGCTATAAAGGGACTTAGCACTGTATGCATAC
TTAAAAGGTTTTTGAAAAACAACTACTTGAGAAATATTTGTTTATATTTTTCTCTAACA
TCATGCTATGTGTGCTGCTGAACATCTGACAACAGAAATTTGAGTTATTATTCTAGCTAA
GTTTTGAAAACATTTGTCATGCTGTTAATAGAAAAGTGAACACAGAGATACTGACTCC
ATTAATAAACCATATTTTGTGCCGTTTTGACTGTTCTGACCAATACTAATGGGAACAAT
TCTTGACGTTTTTCTGTTGCTGATTGTTAACATAGAGCAGTCTCTACACTACCCTGAGGC
AACTCTACATTGGAACACTGAGGCTTACAGCCTGCAAGAGCATCAGAGCTGACCATACAT
TTAAACAGAAATGCTGGTTTATTGTCAAAATCACCAGTATATTTCTATTGTGTCTATAA

FIGURE 107 Continued

AAAATCAGTCATTTAAGTACAAGAATCATATTTTCCATTCCTTTTAGAAATTATTTTG
TTGTCCCTATGGAAATCATTCACATCTGACAATTTATATGTTAAAGAGTTTACTCTCTC
TATTTTGGTCCAATTTGTATCTAGTGGCTGAGAAATTAAATAATTCTAAAGTATGAAGTT
ACCTATCTGAAAATGTACTTACAGAGTATCATTTTAAAATGGATGTCTCTTTAAAAATTT
TGTTACTTTTACCAACAATGTAATATAATTTATGTATATTTTATTAATAATAGTGAATTC
CTTAAAATTTGTTCTATGTACTTATATTTAATTTGATTTAATGGTTACTGCCCAGATATT
GAGAAATGGTTCAAATATTGAGTGTGTTTCAATAA

FIGURE 108

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><Fri Jun 25 15:00:51 PDT 1999 DNA98380 [min]
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA98380
><subunit 1 of 1, 519 aa, 1 stop
><MW: 57552, pI: 10.01, NX(S/T): 3
MTCPDKPGQLINWFICSLCVPRVRKLWSSRRPRTTRNLLLGTAIYLGFLVSQVGRASL
QHGGAAEKGPHRSDTAEPSFPEIPLDGTLPAPPESQNGSTLQPNVVYITLRSKRSPAN
IRGTVKPKRRKKHAVASAPGQEQALVGPSLQPQEAAREADAVAPGYAQGANLVKIGERPW
RLVRGPGVRAGGPDFLQPSSRESNIRIYSESAPSWLSKDDIRRMRLADSAGLRPVSS
RSGARLLVLEGGAPGAVLRCGPSPCGLLKQPLDMSEVFAFHLDRILGLNRTLPSVSRKAE
FIQDGRPCPIILWDASLSSASNDTHSSVKLTWGTYQQLLKQKCWQNGRVKPKPESGCTEIH
HHEWSKMALDFLLQIYNRLDTNCCGFRPRKEDACVQNGLRPKCDDQGSAAAHIIQRKH
DPRHLVFIDNKGFFDRSEDNLNFKLLEGIKEFPASAVSVLKSQHLRQKLLQSLFLDKVYW
ESQGGRQGIEKLIDVIEHRAKILITYINAHGVKVLPMNE
```

FIGURE 109

GGAAAGAGTGCTGGTACTACAACCAGGAAGTGACAGATAATGTGCTTTAACTACATTAG
AAAAGCTTCTCATAGCAAACTGAGAGATTGAAGCAGTGATTATTTTACATAGTTGTCA
TTAAATATTTGGAGCTCTGCTGTGCATAGAGATGGCAACATACTTAGAATACACAGCTTT
CTGGGCCAGAAATTGATCTTCTGACTTTTGAGCCTTATCTGATTACTGCTTGGTTCATCT
TTATTTTGTTAACTACTCTGTAGGCTGAAAGGGAGAGACTCTCCTTGGTTTGCAGAGCC
TGACTAGACAGGAATTCTGGCAACTGCTCCAGCAGAACTATGGCACTGAGCTAGGTTTAA
ATGCTGAGGAGATGGAATACTGTCACTGTGCGATTGAGGATGTGCAGCCAAGAAGTCCAG
GAAGAAGCAGCTTGGATGACTCTGGGGAGAGAGATGAAAAATTATCCAAGTCAATCAGTT
TTACCAGTGAATCAATTAGTCGGGTTTCAGAAACAGAGTCATTTCGATGGAAATTCATCAA
AAGGAGGATTAGGCAAGAGGAGTCCCAAAATGAGAAACAGACCAAAAAGAGTCTCTTAC
CAACTTTGGAAGAAGTTAACTAGAGTGCCATCAAAGTCACTGGACTTGAATAAAAATG
AATATCTTTCTCTGGACAAAAGCAGCACTTCAGATTCTGTTGATGAAGAAAATGTTCTTG
AGAAAGATCTTCATGGAAGACTTTTATCAACCGTATTTTTCATATCAGTGTGCAGAA
TGTTTGAATTGCTCTTTACCAGTTCACGCTTTATGCAGAAATTTGCCAGTTCTAGAAATA
TAATAGATGTAGTATCTACCCCTTGGACTGCAGAACTTGGAGGTGATCAGCTGAGAACGA
TGACCTACACTATAGTCCTTAATAGTCCACTTACTGGAAAATGCACTGCTGCCACTGAAA
AGCAGACACTGTATAAAGAAAGTCGGAAGCACGATTTTATTTGGTAGATTCAGAAGTAC
TGACACATGATGTCCCTACCATGATTACTTCTATACCGTGAACAGATACTGTATCATCC
GATCTTCAAAACAGAAATGCAGGCTAAGAGTTTCCACAGATTTGAAATACAGAAAACAGC
CATGGGGCCTTGTCAAATCTTTAATTGAAAAGAATTCCTGGAGTTCTTTGGAGGACTATT
TCAAACAGCTTGAATCAGATTTGTTAATTGAAGAATCTGTATTAAATCAGGCCATTGAAG
ACCTGGAAAACCTTACTGGCCTACGAAGGAGAAGGCGAACCTTCAACCGAACAGCAGAAA
CAGTTCCTAAACTTTCTCTCAGCATTCTCTGGAGATGTGGGCTTAGGTGCCAAAGGGG
ATATTACAGGAAAGAAAAGGAAATGGAATACTATAACGTCACTCTTATTGTGGTAATGA
GTATTTTGTGTTGTTATTAGTTTGTGTTGAATGTGACACTGTTTCTGAAGCTGTCAAAGA
TAGAACATGCTGCTCAGTCCTTTTACCGTCTCCGCCTCCAAGAAGAGAAATCTTTAAATT
TAGCCTCTGATATGGTGTCAAGAGCAGAACTATTGAGAAGATAAGATCAGGCCCATC
GTTTAAAGGGAGTGCTCCGAGACTCCATAGTGATGCTTGAACAGCTGAAGAGCTCACTCA
TTATGCTTCAGAAAACGTTTGATCTACTAAATAAGAATAAGACTGGCATGGCTGTTGAAA
GCTAGTGATCTGAAGGACTAAAACCGCAGAGATACTTGGAACTTAAAGAAAATACCTGGA
AGAAAACCAGACGAATGAAGGATTTTGGCATAGAACATTTCTATGTTTTTTCATTATTGA
GATTTCTAATATGAACATTTCTTTCAGTAACATTTATTTGATAATTAGTTTCTGCTGGCC
TTAATAATCCATCCTTTCACTTCTTATAGATATTTTAAAGCTGTGAATTTCTTCAGTGAA
CCATGAAATATATATAGAACTGAATTTCTCTGATACAAAAGAAAATGACACACCCTGA
ATTGAGTGGTATGGTCTCATTTCTACAGTGAAGTCTGATGCTTTGTTAGCACAGAATCCG
TACATGTCCAATAGGTGCTTTTGTAACTGAGATAAGACCAAGAGGATAAACAGGACAAT
ATAAGAAGAAACCTCTATGTCACTTACTGATTTTAAAGGTTCTGTTTTTCAGGCATATAACA
TTTCCAGGTTTGTGTAAGATTATAATGTCTTCATTTATTTAGCATGCAAATTTA
ATAGTCAAACCTTTTGAATCTGCATGTTGATGATGATTATCAGAAAGGGTCTTCTGCCAT
GCTGTATCTTTATGAAAGAAAATAGTTGTTTTTCTTAAGGTAACATCAGAGGTGGGATT
ATCTTGCCCTCCTCACTTAGAATACCAACAGTCAAAGGAAGAACCATCCTCTGAGTTTAA
AAAACCAGAAGGTTATGTTAAAATCTGGGCATTTAGTGACAGATCAAATGCATACTTGAA

FIGURE 109 Continued

CTAAGATTGGCTTCAGCTTAGCAGTCTTTCATGGTGGAAGTGACACATCTGGTTGAAAAT
AATTTGTGTATTTTCAGTAACCATGTATGGCTTCCTTCTTTATGTATGTGTGTGACTTGT
TTTAATTGGTAAGTTATAAGCCAGACATAGATTTTAGCTCTTTAATAAAAACCTTCAGGGG
CACGTATGTCCAGTACAAGTGACTGACTATCAAGTTTTAACTCAGATGCAAGCTTTGG
CTCTTTCATAAAAAGTTTTATGCATATGTGTCTCCATACAAGTGGCTCATTAAAATAAG
AACTTTGTAACTGACTTAAATCAGATATTTTTCAAGAGTTAGGGAAAGTTGAAGTGT
TTTACTGTTTTGTCTCTTGAGCCCTTCTCTGGGGAAAAATACATATCCATCTATCTAT
CTATATATAAACTGTGTATACATTCTTACTGTTTGAACAACCTATTGCCTTTAATTAAATG
TTTCATTTTTCTCCAGAGTCCCCAAAGCCACATGGCATTATTATAGTCATTTTTGAGATG
CCTGTAGAGAATGAAAGTATTGACTCCGTTAGAGGGAAAATGGGTTTCTCTGGGTGAATT
CCAACGAAGCATACCTAGGGGTAACAGTGAACCTACCTGGGTTTGTGTTTTGGTAAG
GATTTATGTAGTGTCTGGCTGTAAGCAAGAATGAGTGGATTATAAACTTGAAGATTCTC
TGTTAAAGTCACAAAATGATCGACAAACAATATTTTGTGATGTTATTTAAACGTTGT
ATTTTATAACATACTTCAAGGAAGAGTATCGAAGTAAGTTGCTTTATAAATTAAGACTAA
ATTTCGTATGGATGCAGAAATCAATTAATAAAATTTGAGCCTGTTACGTAAATTGAATATT
AATAAAATTGAAAATTTCAAAA

FIGURE 110

MENLSLSIEDVQPRSPGRSSLDSDGERDEKLSKSI SFTSESISRVS ETESFDGNSSKGGL
 GKEESQNEKQTKKSLPTLEKKLTRVPSKSLDLNKNEYLSDKSSTSDSVDEENVPEKDL
 HGRLF INRIFHISADRMFELLFTSSRFMQKFASSRNIIDVSTPWTAE LGGDQLRTMTYT
 IVLNSPLTGKCTAATEKQ TLYKESREARFYLVDSEVLTHDVPYHDYFYTVNRYCIIRSSK
 QKCR LRVSTDLKYRKQPWGLVKSLIEKNSWSSLEDYFKQLES DLLIEESVLNQAIEDPGK
 LTGLRRRRRTFNRTAETVPKLSSQHSSGDVGLGAKGDITGKKKEMENYNVTLIVMSIFV
 LLLVLLNVTLFLKLSKIEHAAQSFYRLRLQEEKSLNLASDMVSRAETIQKNKDAQHRLKG
 VLRDSIVMLEQLKSS LIMLQKTFDLLNKNKTGM AVES

3-7 N-glycosylation site
 54-58 N-glycosylation site
 312-316 N-glycosylation site
 349-353 N-glycosylation site
 367-371 N-glycosylation site
 449-453 N-glycosylation site

81-85 cAMP- and cGMP-dependent protein kinase
 phosphorylation site
 307-311 cAMP- and cGMP-dependent protein kinase
 phosphorylation site

7-11 Casein kinase II phosphorylation site
 19-23 Casein kinase II phosphorylation site
 20-24 Casein kinase II phosphorylation site
 46-50 Casein kinase II phosphorylation site
 65-69 Casein kinase II phosphorylation site
 105-109 Casein kinase II phosphorylation site
 109-113 Casein kinase II phosphorylation site
 263-267 Casein kinase II phosphorylation site
 271-275 Casein kinase II phosphorylation site
 272-276 Casein kinase II phosphorylation site
 326-330 Casein kinase II phosphorylation site
 375-379 Casein kinase II phosphorylation site
 403-407 Casein kinase II phosphorylation site

202-211 Tyrosine kinase phosphorylation site
 246-255 Tyrosine kinase phosphorylation site
 341-350 Tyrosine kinase phosphorylation site

259-265 N-myristoylation site

339-343 Amidation site

FIGURE 111

CGGACGCGTG GGGGCCGTATGCGCGGCTCTGTGGAGTGCACCTGGGGTTGGGGGCACTGTG
CCCCAGCCCCCTGCTCCTTTGGACTCTACTTCTGTTTGCAGCCCCATTTGGCCTGCTGG
GGGAGAAGACCCGCCAGGTGTCTCTGGAGGTCTATCCCTAACTGGCTGGGCCCCCTGCAGA
ACCTGCTTCATATACGGGCAGTGGGCACCAATTCCACACTGCACTATGTGTGGAGCAGCC
TGGGGCCTCTGGCAGTGGTAATGGTGGCCACCAACACCCCCACAGCACCTTGAGCATCA
ACTGGAGCCTCCTGCTATCCCCTGAGCCCGATGGGGGCTGATGGTGTCTCCCTAAGGACA
GCATTTCAGTTTTCTTCTGCCCTTGTTTTTACCAGGCTGCTTGAGTTTGACAGCACCAACG
TGTCCGATACGGCAGCAAAGCCTTTGGGAAGACCATATCCTCCATACTCCTTGCCCGATT
TCTCTTGGAACAACATCACTGATTCATTGGATCCTGCCACCCTGAGTGCCACATTTCAAG
GCCACCCCATGAACGACCCTACCAGGACTTTTGCCAATGGCAGCCTGGCCTTCAGGGTCC
AGGCCTTTTCCAGGTCCAGCCGACCAGCCCAACCCCTCGCCTCCTGCACACAGCAGACA
CCTGTCAGCTAGAGGTGGCCCTGATTGGAGCCTCTCCCCGGGGAAACCGTTCCCTGTTTG
GGCTGGAGGTAGCCACATTGGGCCAGGGCCCTGACTGCCCCCTCAATGCAGGAGCAGCACT
CCATCGACGATGAATATGCACCGGCCGTCTTCCAGTTGGACCAGCTACTGTGGGGCTCCC
TCCCATCAGGCTTTGCACAGTGGCGACCAGTGGCTTACTCCCAGAAGCCGGGGGGCCGAG
AATCAGCCCTGCCCTGCCAAGCTTCCCCTCTTCATCCTGCCTTAGCATACTCTCTTCCCC
AGTCACCCATTGTCCGAGCCTTCTTTGGGTCCCAGAATAACTTCTGTGCCTTCAATCTGA
CGTTCGGGGCTTCCACAGGCCCTGGCTATTGGGACCAACACTACCTCAGCTGGTCGATGC
TCCTGGGTGTGGGCTTCCCTCCAGTGGACGGCTTGTCCCCACTAGTCCTGGGCATCATGG
CAGTGGCCCTGGGTGCCCCAGGGCTCATGCTGCTAGGGGGCGGCTTGTTTCTGCTGCTGC
ACCACAAGAAGTACTCAGAGTACCAGTCCATAAATTAAAGGCCCGCTCTCTGGAGGGAAGG
ACATTACTGAACCTGTCTTGCTGTGCCTCGAAACTCTGGAGGTTGGAGCATCAAGTTCCA
GCCGGCCCCCTTCACTCCCCCATCTTGCTTTTTCTGTGGAACCTCAGAGGCCAGCCTCGACT
TCCTGGAGACCCCCAGGTGGGGCTTCCTTCATACTTTGTTGGGGGACTTTGGAGGCGGGC
AGGGGACAGGGCTATTGATAAGGTCCCCTTGGTGTGCTTCTTGATCTCCACACATTT
CCCTTGATGGGACTTGCAGGCCTAAATGAGAGGCATTCTGACTGGTTGGCTGCCCTGGA
AGGCAAGAAAATAGATTTATTTTTTTTTCACAGGGAAAAAAAAAAAAA

FIGURE 112

MRGSVECTWGWGHCAPSPLLLWTLTLLFAAPFGLLGKTRQVSLEVIPNWLGPLQNLLHIR
 AVGTNSTLHYVWSSLGPLAVVMVATNTPHSTLSINWSLLLSPEPDGGLMVLPKDSIQFSS
 ALVFTRLLEFDSTNVSDTAAKPLGRPYPPYSLADFSWNNITDSLDPATLSATFQGHMND
 PTRTFANGSLAFRVQAFSRSSRPAQPPRLHTADTCQLEVALIGASPRGNRSLEFGLEVAT
 LGQGPDCPSMQEQHSIDDEYAPAVFQLDQLLWGSLLPSGFAQWRPVAYSQKPGGRESALPC
 QASPLHPALAYSLPQSPIVRAFFGSQNNFCFNLTFGASTGPGYWDQHLYLSWSMLLGVG
 PPVDGLSPLVLGIMAVALGAPGLMLLGGGLVLLLHHKKYSEYQSIN

65-69	N-glycosylation site
95-99	N-glycosylation site
134-138	N-glycosylation site
159-163	N-glycosylation site
187-191	N-glycosylation site
230-234	N-glycosylation site
333-337	N-glycosylation site
397-401	cAMP- and cGMP-dependent protein kinase phosphorylation site
151-155	Casein kinase II phosphorylation site
249-253	Casein kinase II phosphorylation site
255-259	Casein kinase II phosphorylation site
3-9	N-myristoylation site
63-69	N-myristoylation site
235-241	N-myristoylation site
273-279	N-myristoylation site
292-298	N-myristoylation site
324-330	N-myristoylation site
371-393	Leucine zipper pattern

FIGURE 113

GGAAAAGGTACCCGCGAGAGACAGCCAGCAGTTCTGTGGAGCAGCGGTGGCCGGCTAGGA
TGGGCTGTCTCTGGGGTCTGGCTCTGCCCCCTTTCTTCTTCTGCTGGGAGGTTGGGGTCT
CTGGGAGCTCTGCAGGCCCCAGCACCCGCGAGAGCAGACACTGCGATGACAACGGACGACA
CAGAAGTGCCCGCTATGACTCTAGCACCCGGGCCACGCCGCTCTGGAACTCAAACGCTGA
GCGCTGAGACCTCTTCTAGGGCCTCAACCCAGCCGGCCCCATTCCAGAAGCAGAGACCA
GGGGAGCCAAGAGAATTTCCCTGCAAGAGAGACCAGGAGTTTCAAAAAACATCTCCCA
ACTTCATGGTGCTGATCGCCACCTCCGTGGAGACATCAGCCGCCAGTGGCAGCCCCGAGG
GAGCTGGAATGACCACAGTTCAGACCATCACAGGCAGTGATCCCGAGGAAGCCATCTTTG
ACACCCCTTTGCACCGATGACAGCTCTGAAGAGGCAAAGACACTCACAATGGACATATTGA
CATTGGCTCACACCTCCACAGAAGCTAAGGGCCTGTCTCAGAGAGCAGTGCCCTCTTCCG
ACGGCCCCCATCCAGTCATCACCCCGTCACGGGCCTCAGAGAGCAGCGCCTCTTCCGACG
GCCCCCATCCAGTCATCACCCCGTCACGGGCCTCAGAGAGCAGCGCCTCTTCCGACGGCC
CCCATCCAGTCATCACCCCGTCATGGTCCCCGGGATCTGATGTCACTCTCTCGCTGAAG
CCCTGGTGACTGTCAAAACATCGAGGTTATTAATTGCAGCATCACAGAAATAGAAACAA
CAACTTCCAGCATCCCTGGGGCCTCAGACATAGATCTCATCCCCACGGAAGGGGTGAAGG
CCTCGTCCACCTCCGATCCACCAGCTCTGCCTGACTCCACTGAAGCAAACACACATCA
CTGAGGTACAGCCTCTGCCGAGACCCTGTCCACAGCCGGCACCACAGAGTCAGCTGCAC
CTCATGCCACGGTTGGGACCCCACTCCCCACTAACAGCGCCACAGAAAGAGAAGTGACAG
CACCCGGGGCCACGACCCCTCAGTGGAGCTCTGGTCACAGTTAGCAGGAATCCCCTGGAAG
AAACCTCAGCCCTCTCTGTTGAGACACCAAGTTACGTCAAAGTCTCAGGAGCAGCTCCGG
TCTCCATAGAGGCTGGGTGAGCAGTGGGCAAAACAACCTTCCTTTGCTGGGAGCTCTGCTT
CCTCCTACAGCCCTCGGAAGCCGCCCTCAAGAACCTCACCCCTTCAGAGACACCGACCA
TGGACATCGCAACCAAGGGGCCCTTCCCCACCAGCAGGGACCCTCTTCCTTCTGTCCCTC
CGACTACAACCAACAGCAGCCGAGGGACGAACAGCACCTTAGCCAAGATCACAACCTCAG
CGAAGACCACGATGAAGCCCCAACAGCCACGCCCACGACTGCCCGGACGAGGCCGACCAC
AGACGTGAGTGCAGGTGAAAATGGAGGTTTCCTCCTCCTGCGGCTGAGTGTGGCTTCCCC
GGAAGACCTCACTGACCCCAGAGTGGCAGAAAGGCTGATGCAGCAGCTCCACCGGGAAC
CCACGCCCACGCGCCTCACTTCAGGTCCTTACTGCGTGTGAGGAGGCTAACGGAC
ATCAGCTGCAGCCAGGCATGTCCCGTATGCCAAAAGAGGGTGCTGCCCTAGCCTGGGCC
CCCACCGACAGACTGCAGCTGCGTTACTGTGCTGAGAGGTACCCAGAAGGTTCCCATGAA
GGGCAGCATGTCCAAGCCCCTAACCCAGATGTGGCAACAGGACCTCGCTCACATCCAC
CGGAGTGTATGTATGGGGAGGGGCTTCACCTGTTCCAGAGGTGTCTTGGACTCACCTT
GGCATATGTTCTGTGTTTCAGTAAAGAGAGACCTGATCACCCATCTGTGTGCTTCCATCC
TGCAATAAAATCACTCAGTGTGGCCCAAAAAA

FIGURE 114

MGCLWGLALPLFFFCWEVGVSGSSAGPSTRRADTAMTTDDTEVPAMTLAPGHAALETQTL
 SAETSSRASTPAGPIPEAETRGAKRISPARETRSFTKTSNFMVLIATSVETSAASGSPE
 GAGMTTVQTITGSDPEEAIFDTLCTDDSSSEEAKLTMDILTLAHTSTEAKGLSSESSASS
 DGPHPVITPSRASESSASSDGPHPVITPSRASESSASSDGPHPVITPSWSPGSDVTLLE
 ALVTVTNIEVINCSITEIETTTSSIPGASDIDLIPTEGVKASSTSDPPALPDSTEAKPHI
 TEVTASAETLSTAGTTESAAPHATVGTPLPTNSATEREVTAPGATTLSGALVTVSRNPLE
 ETSALSVETPSYVKVSGAAPVSI EAGSAVGKTTSFAGSSASSYSPSEALKNFTPSETPT
 MDIATKGFPFPTS RDPLPSVPPTTTNSSRGTNSTLAKITTS AKTTMKPQQPRRLPGRGRP
 QT

252-256	N-glycosylation site
445-449	N-glycosylation site
451-455	N-glycosylation site
84-90	cAMP-and cGMP-dependent protein kinase phosphorylation site
37 -41	Casein kinase II phosphorylation site
108-112	Casein kinase II phosphorylation site
131-135	Casein kinase II phosphorylation site
133-137	Casein kinase II phosphorylation site
148-152	Casein kinase II phosphorylation site
165-169	Casein kinase II phosphorylation site
246-250	Casein kinase II phosphorylation site
254-258	Casein kinase II phosphorylation site
256-260	Casein kinase II phosphorylation site
269-273	Casein kinase II phosphorylation site
283-287	Casein kinase II phosphorylation site
333-337	Casein kinase II phosphorylation site
335-339	Casein kinase II phosphorylation site
404-408	Casein kinase II phosphorylation site
414-418	Casein kinase II phosphorylation site
431-435	Casein kinase II phosphorylation site
2-8	N-myristoylation site
19-25	N-myristoylation site
117-123	N-myristoylation site
121-127	N-myristoylation site
232-238	N-myristoylation site
278-284	N-myristoylation site
314-320	N-myristoylation site
349-355	N-myristoylation site
386-392	N-myristoylation site
397-403	N-myristoylation site
449-455	N-myristoylation site
385-393	ATP/GTP-binding site motif A (P-loop)

FIGURE 115

GCGAGGCGGCGCTGTCTTCTGCTGCGGCTTCCGCGACCACAAGTACTGCTGCGACGACC
CGCACAGCTTCTTCCCCTACGAGCACAGCTACATGTGGTGGCTCAGCATTGGCGCTCTCA
TAGGCCTGTCCGTAGCAGCAGTGGTTCTTCTCGCCTTCATTGTTACCGCCTGTGTGCTCT
GCTACCTGTTTCATCAGCTCTAAGCCCCACACAAAGTTGGACCTGGGCTTGAGCTTACAGA
CAGCAGGCCCTGAGGAGGTTTCTCCTGACTGCCAAGGTGTGAACACAGGCATGGCGGCAG
AAGTGCCAAAAGTGAGCCCTCTCCAGCAGAGTTACTCCTGCTTGAACCCGCAGCTGGAGA
GCAATGAGGGGCAGGCTGTGAACTCCAAACGCCTCCTCCATCATTGCTTCATGGCCACAG
TGACCACCAGTGACATTCCAGGCAGCCCTGAGGAAGCCTCTGTACCCAACCCTGACCTAT
GTGGACCAGTCCCTAAACATTCAATAAATGTCTCCATACCATCAA

FIGURE 116

MWWLSIGALIGLSVAAVVLLAFIVTACVLCYLFISSKPHTKLDLGLSLQTAGPEEVSPDC
QGVNTGMAAEVPKVSPLQQSYSCLNPQLESNEGQAVNSKRLLLHCFMATVTTSDIPGSPE
EASVPNPDLCGPVP

40-44	Casein kinase II phosphorylation site
111-115	Casein kinase II phosphorylation site
118-122	Casein kinase II phosphorylation site
7-13	N-myristoylation site
11-17	N-myristoylation site
62-68	N-myristoylation site
93-99	N-myristoylation site
17-28	Prokaryotic membrane lipoprotein lipid attachment site

FIGURE 117

CCTCTGTCTGTGCTCCCATCCCAGGGAGTATAGGTGGAGCCTCCAGAGCCCATGGACAGG
GCATGCTGGGGCTGGGCCAGCCCCAGCGGTGTCTCTAAGGCACCCCTGGGATCCCCACTG
AGCTGGCCTACTTCAGACAGCCAGGGGCCACCCCTCTGGCCCCCTTAGTGTCCAGCTCGT
GGCCCCCTTGGCATTTCACAAAGACGCCAAGATGGAGATTCCCATGGGGACCCAGGGCTGC
TTCTCAAAGAGCCTCCTGCTCTCAGCCTCAATCCTGGTCTCTGGATGCTCCAAGGCTCC
CAGGCAGCTCTCTACATCCAGAAGATTCCAGAGCAGCCTCAAAAGAACCAGGACCTTCTC
CTGTCACTCCAGGGTGTCCAGACACCTTCCAGGACTTCAACTGGTACCTGGGGGAGGAG
ACGTACGGAGGCACGAGGCTATTTACCTACATCCCTGGGATACAACGGCCTCAGAGGGAT
GGCAGTGCCATGGGACAGCGAGACATCGTGGGCTTCCCCAATGGTTCCATGTGCTGCGC
CGCGCCAGCCTACAGACAGTGGCACCTACCAAGTAGCCATTACCATCAACTCTGAATGG
ACTATGAAGGCCAAGACTGAGGTCCAGGTAGCTGAAAAGAATAAGGAGCTGCCAGTACA
CACCTGCCCACCAACGCTGGGATCCTGGCGGCCACCATCATTGGATCTCTTGCTGCCGGG
GCCCTTCTCATCAGCTGCATTGCCATCTCTCTGGTGACAAGGAACTGGAGGGGCCAGAGC
CACAGACTGCCTGCTCCGAGGGGCCAGGGATCTCTGTCCATCTTGTGCTCGGCTGTATCC
CCAGTGCCCTTCAGTGACGCCAGCACATGGATGGCGACCACAGAGAAGCCAGAATTGGGC
CCTGCTCATGATGCTGGTGACAACAACATCTATGAAGTGATGCCCTCTCCAGTCTCCTG
GTGTCCCCCATCAGTGACACAAGGTCCATAAACCCAGCCCGGCCCTGCCACACCCCCA
CACCTGCAGGCGGAGCCAGAGAACCACAGTACCAGCAGGACCTGCTAAACCCGACCCCT
GCCCCCTACTGCCAGCTGGTGCCAACTTCTGATGGGTCTCTGGGCCAGGCCAGCCAGGGA
GAAGACAAGGCCCCAGCCCTCCTCTGGGAGCCTCACACCTGAGACCAGCAGGACAAGGCC
ATTGGGGGCTGTGGGGCCGATGAGGTGGACTCAGCCAAAGACTCAGCAGCACATGGGGCA
GGTGTCTTGGCAGGGGGACAGGAGACTGTAACAGGCCCAGGTCTTGTGCAGCCCTGAA
TGCACGCCCCGCTTCGGTCTGTTCCCTCAAGCAAGCTGGCCTGGGCCATGTGCCTGTGAA
AGGCAGGCTCTGGCCCCCTTCCATGCCAAAGTCCCCCAAGATCTGGATATCTGGGGACAA
GATGGTGGCCTCAGGCCTGCCTCCAGGCAGTTGGCTGGGCTCCCAACTGTCTGTCTCTCA
ATGCCCTACCCCAACTCCACTAGTGACCCCTCAGAGTCTTCTCCCTTAGGACAAGGCAGA
CACCCCACCATGCGGGCCTCAGGTGGCAGAGAGGCCAGCCTCACAGGCCTGTGGCCCCA
CACACAGTCCCAGCAAGGTGACCAGGCTGCTGGACCCCTTCCCTGTTCAAGCAGGCCC
AGCCCCCTCTCAGAACCTGTGTCAGCTGCTGGTCTTGGCCCCCACCCTGAATCTTACTGA
GTCCCTCTGGGCAGCAGCTCCCTTCTCCACCCACCCAGCACCCGTCCCAAATGTGGCC
TCAGCTTGCTCTCCCTTCCCCAACTATGCATTATTAGCAATAAATGAGCCTTTGCT
GCA

FIGURE 118

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><Wed Aug 18 11:18:02 PDT 1999 DNA119535 [min]
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA119535
><subunit 1 of 1, 300 aa, 1 stop
><MW: 32638, pI: 6.02, NX(S/T): 1
MEIPMGTTGGCFSKSLLLSASILVLWMLQGSQAALYIQKIPEQPQKNQDLLLSVQGVPDF
QDFNWYLGEETYGGTRLFTYIPGIQRPQRDGSAMGQRDIVGFNGSM LLRRAQPTDSGT
YQVAITINSEWTMKAKTEVQVAEKNKELPSTHLPTNAGILAATIIGSLAAGALLISCIAYL
LVTRNWRGQSHRLPAPRGQGSLSILCSAVSPVPSVTPSTWMATTEKPELGPAMDAGDNNI
YEVMPSPVLLVSPISDTRSINPARPLPTPPHLQAEFENHQQDLLNPDPAFYCQLVPTS
```

FIGURE 119

AGCATGAGAGGCCTGGCCGTCCTCCTCACTGTGGCTCTGGCCACGCTCCTGGCTCCCGGG
GCCGGAGCACCGGTACAAAGTCAGGGCTCCCAGAACAAAGCTGCTCCTGGTGTCTTCGAC
GGCTTCCGCTGGAACTACGACCAGGATGTGGACACCCCCAACCTGGACGCCATGGCCCCGA
GACGGGGTGAAGGCACGCTACATGACCCCCGCCTTTGTCACCATGACCAGCCCCCTGCCAC
TTCACCCTGGTCACCGGCAAATATATCGAGAACACGGGGTGGTTACAACATGTACTAC
AACATCACCAGCAAGGTGAAGCTGCCTACCACGCCACGCTGGGCATCCAGAGGTGGTGG
GACAACGGCAGCGTGCCCATCTGGATCACAGCCAGAGGCAGGGCCTGAGGGCTGGCTCC
TTCTTCTACCCGGGCGGGAACGTACCTACCAAGGGTGGCTGTGACGCGGAGCCGGA
GAAGGCATCGCACACAATACTACAAAAATGAGACGGAGTGGAGAGCGAACATCGACACAGTG
ATGGCGTGGTTACAGAGGAGGACCTGGATCTGGTCACACTCTACTTCGGGGAGCCGGAC
TCCACGGGCCACAGGTACGGCCCCGAGTCCCCGGAGAGGAGGGAGATGGTGCAGGAGGTG
GACCGGACCGTGGGCTACCTCCGGGAGAGCATCGCGCGCAACCACCTCACAGACCGCCTC
AACCTGATCATCACATCCGACCACGGCATGACGACCGTGGACAAACGGGCTGGCGACCTG
GTTGAATTCCACAAGTTCCCCAACTTCACCTTCGGGACATCGAGTTTGAGCTCCTGGAC
TACGGACCAAACGGGATGCTGCTCCCTAAAGAAGGGAGGCTGGAGAAGGTGTACGATGCC
CTCAAGGACGCCCAACCCCAAGCTCCACGTCTACAAGAAGGAGGCGTTCCCCGAGGCCTTC
CACTACGCCAACAAACCCAGGGTCACACCCCTGCTGATGTACAGCGACCTTGGCTACGTC
ATCCATGGGAGAATTAACGTCCAGTTCAACAATGGGGAGCACGGCTTTGACAACAAGGAC
ATGGACATGAAGACCATCTTCCGCGCTGTGGGCCCTAGCTTCAGGGCGGGCCTGGAGGTG
GAGCCCTTTGAGAGCGTCCACGTGTACGAGCTCATGTGCCGGCTGCTGGGCATCGTGCCC
GAGGCCAACGATGGGCACCTAGCTACTCTGCTGCCCATGCTGCACACAGAATCTGCTCTT
CCGCTGATGGAAGGCCTACTCTCCTGCCCAAGGGAAGATCTGCTCTCCGCCCAGCAGC
AGGCCCTCCTCGTGATGGGACTGCTGGGGACCGTGATTCTTCTGTCTGAGGTTCGCATAA
CGCCCCATGGCTCAAGGAAGCCGCCGGGAGCTGCCCGCAGGCCCTGGGCCGGCTGTCTCG
CTGCGATGCTCTGCTGGTCGCGGACGGACCTGCCTCCCCAGCTTATCCCAGGCCAGAGG
CTGCATGCCACTGTCCCCGGCAGCGCCAACCCCTGCTTGGCTGTTATGGTGTGGTAATA
AGCCTCGCAGCCCAGGTCCAGAGCCCCCGCGAGCCGGTCCCATAACCGGCCCCCTGCCC
CTGCCCTGCTCCTGCTCCTCCCTTCGGGCCCCCTCCTCCTGCAAAACCGCTCCCGAA
GCGGGCGCTGCCGTCTGCAGCCACGCGGGGCGCGCGGGAGCTCTGCGGGCGCTGGAACCT
GCAGACCCGGCCTCGGTCAAGTGGGAGGGGCCCGCCCCGGCACAAAGCACCCATGGGAAT
AAAGGCCAAGCCGCGACAGTCAAAAAAAA

FIGURE 120

MRGLAVLLTVALATLLAPGAGAPVQSQGSQNKLLVVSFDGFRWNYDQDVTNLDAMARD
GVKARYMTPAFVMTSPCHFTLVTKYIENHGVVHNMYNITSKVKLPHYATLGIQRWWD
NGSVPIWITAQRQGLRAGSFFYPGGNVITYQGVAVTRSRKEGIAHNYKNETEWRANIDTVM
AWFTEEDLDLVTLTYFGEPDSTGHRYPESPERRMVRQVDRTVGYLRESIARNHLTDRLN
LIITSDHGMTTVDKRAGDLVEFHKFPNFTFRDIEFELLDYGPNGMLLPKEGRLEKVYDAL
KDAHPKLVHYKKEAFPEAFHYANNPRVTPLLMYSDLGVIHGRINVQFNNGEHGFDNKDM
DMKTI FRAVGPSFRAGLEVPEFESVHVYELMCRLLGIVPEANDGHLATLLPMLHTESALP
PDGRPTLLPKGRSALPPSSRPLLVMGLLGTVILLSEVA

Important features of the protein:
Signal peptide:

1-22

Transmembrane domain:

None

Motif name: N-glycosylation site.

100-104
121-125
146-150
168-172
267-271

Motif name: N-myristoylation site.

92-98
134-140
144-150
151-157
161-167
446-452

Motif name: Leucine zipper pattern.

286-308

FIGURE 121

GCGGCAGCAGCGCGGGCCCCAGCAGCCTCGGCAGCCACAGCCGCTGCAGCCGGGGCAGCC
TCCGCTGCTGTGCGCTCCTCTGATGCGCTTGCCCTCTCCCGCCCCGGGACTCCGGGAGA
ATGTGGGTCCTAGGCATCGCGGCAACTTTTTCGGATTGTTCTTGCTTCCAGGCTTTGCG
CTGCAAATCCAGTGCTACCAAGTGTGAAGAATTCCAGCTGAACAACGACTGCTCCTCCCC
GAGTTCATTGTGAATTGCACGGTGAACGTTCAAGACATGTGTGAGAAAGAAGTGATGGAG
CAAAGTGCCGGGATCATGTACCGCAAGTCTGTGCATCATCAGCGGCCTGTCTCATCGCC
TCTGCCGGGTACCAGTCTTCTGCTCCCCAGGGAAACTGAACTCAGTTTGCATCAGCTGC
TGCAACACCCCTCTTTGTAACGGGCCAAGGCCAAGAAAAGGGGAAGTTCTGCCTCGGCC
CTCAGGCCAGGGCTCCGCACCACCATCCTGTTCTCAAATTAGCCCTCTTCTCGGCACAC
TGCTGAAGCTGAAGGAGATGCCACCCCTCCTGCATTGTTCTTCCAGCCCTCGCCCCAA
CCCCCACCTCCCTGAGTGAGTTTCTTCTGGGTGTCCTTTATTCTGGGTAGGGAGCGGG
AGTCCGTGTTCTCTTTGTTCTGTGCAAATAATGAAAGAGCTCGGTAAAGCATTCTGAA
TAAATTCAGCCTGACTGAATTTTCAGTATGTACTTGAAGGAAGGAGGTGGAGTGAAGTT
CACCCCATGTCTGTGTAACCGGAGTCAAGGCCAGGCTGGCAGAGTCAGTCTTAGAAGT
CACTGAGGTGGGCATCTGCCTTTTGTAAAGCCTCCAGTGTCCATTCCATCCCTGATGGGG
GCATAGTTTGAGACTGCAGAGTGAGAGTGACGTTTCTTAGGGCTGGAGGGCCAGTTCCC
ACTCAAGGCTCCCTCGCTTGACATTCAAACCTCATGCTCCTGAAAACCATCTCTGCAGC
AGAATTGGCTGGTTTCGCGCCTGAGTTGGGCTCTAGTGAAGTCAATGACTGGGA
CTTAGACTGGGGCTCGGCCTCGCTCTGAAAAGTGCTTAAGAAAATCTTCTCAGTTCTCCT
TGCAGAGGACTGGCGCCGGGACGCGAAGAGCAACGGGCGCTGCACAAAGCGGGCGCTGTC
GGTGGTGGAGTGCGCATGTACGCGCAGGCGCTTCTCGTGGTTGGCGTGCTGCAGCGACAG
GCGGCAGCACAGCACCTGCACGAACACCGCCGAAACTGCTGCGAGGACACCGTGTACAG
GAGCGGGTTGATGACCGAGCTGAGGTAGAAAAACGTCTCCGAGAAGGGGAGGAGGATCAT
GTACGCCCGGAAGTAGGACCTCGTCCAGTCGTGCTTGGGTTTGGCCGAGCCATGATCCT
CCGAATCTGGTTGGGCATCCAGCATACGGCCAATGTCAACAATCAGCCCTGGGCAGAC
ACGAGCAGGAGGGAGAGACAGAGA

FIGURE 122

MWVLGIAATFCGLFLLPGFALQIQCYQCEEFQLNNDCSSPEFIVNCTVNVQDMCQKEVME
QSAGIMYRKSCASSAACLIASAGYQSFCSPGKLNSVCISCCNTPLCNGPRPKKRGSSASA
LRPGLRTTILFLKLALFSAHC

Important features of the protein:
Signal peptide:

1-22

Transmembrane domain:

None

Motif name: N-glycosylation site.

45-49

Motif name: cAMP- and cGMP-dependent protein kinase phosphorylation site.

113-117

Motif name: N-myristoylation site.

5-11

115-121

124-130

Motif name: Ly-6 / u-PAR domain proteins

94-107

FIGURE 123

AGCACTCTCCAGCCTCTCACCGCAAAATTACACACCCAGTACACCAGCAGAGGAACTT
ATAACCTCGGGAGGCGGGTCCTTCCCCTCAGTGCAGTACATACTTCCAGAAGAGCGGAC
CAGGGCTGCTGCCAGCACCTGCCACTCAGAGCGCCTCTGTGCTGGGACCCCTCAGAACT
CTCTTTGCTCACAAGTTACCAAAAAAAAAAGAGCCAACATGTTGGTATTGCTGGCTGGTA
TCTTTGTGGTCCACATCGCTACTGTTATTATGCTATTTGTTAGCACCATTGCCAATGTCT
GGTTGGTTTCCAATACGGTAGATGCATCAGTAGGTCTTTGGAAAACTGTACCAACATTA
GCTGCAGTGACAGCCTGTCTATATGCCAGTGAAGATGCCCTCAAGACAGTGCAGGCCTTCA
TGATTCTCTCTATCATCTTCTGTGTCAATTGCCCTCCTGGTCTTCGTGTTCCAGCTCTTCA
CCATGGAGAAGGGAAACCGGTTCTTCTCTCAGGGGCCACCACACTGGTGTGCTGGCTGT
GCATTCTTGTGGGGGTGTCCATCTACACTAGTCATTATGCGAATCGTGATGGAACGCAGT
ATCACCACGGCTATTCTACATCCTGGGCTGGATCTGCTTCTGCTTCAGCTTCATCATCG
GCGTTCTCTATCTGGTCTGAGAAAGAAATAAGGCCGACGAGTTCATGGGGATCTGGGG
GGTGGGGAGGAGGAAGCCGTTGAATCTGGGAGGGAAGTGGAGGTTGCTGTACAGGAAAAA
CCGAGATAGGGGAGGGGGAGGGGGAAGCAAAGGGGGGAGGTCAAATCCCAAACCATTAC
TGAGGGGATTTCTCTACTGCCAAGCCCCTGCCCTGGGGAGAAAGTAGTTGGCTAGTACTTT
GATGCTCCCTTGATGGGGTCCAGAGAGCCTCCCTGCAGCCACCAGACTTGGCCTCCAGCT
GTTCTTAGTGACACACACTGTCTGGGGCCCCATCAGCTGCCACAACACCAGCCCCACTTC
TGGGTCTATGCACTGAGGTCCACAGACCTACTGCACTGAGTTAAAAAGCGGTACAAGTTC
TGGCAAGAGCAGATACTGTCTTTGTGCTGAATACGCTAAGCCTGGAAGCCATCCTGCCCT
TCTGACCCAAAGCAAAACATCACATTCAGTCTGAAGTGCCTACTGGGGGGCTTTGGCCT
GTGAGCCATTGTCCCTCTTTGGAACAGATATTTAGCTCTGTGGAATTCAGTGACAAAATG
GGAGGAGGAAAGAGAGTTTGTAAAGTCATGCTGGTGGGTTAGCTAAACCAAGAAGGAGAC
CTTTTCACAATGGAACCTGGGGGATGGTCAGAGCCCAGTCGAGACCTCACACACGGCT
GTCCCTCATGGAGACCTCATGCCATGGTCTTTGCTAGGCCTCTTGCTGAAAGCCAAGGCA
GCTCTTCTGGAGTTTCTCTAAAGTCACTAGTGAACAATTCGGTGGTAAAAGTACCACACA
AACTATGGGATCCAAGGGGCAGTCTTGCAACAGTGCCATGTTAGGGTTATGTTTTTAGGA
TTCCCTCAATGCAGTCAGTGTCTTTTAAAGTATACAACAGGAGAGAGATGGACATGGC
TCATTGTAGCACAATCCTATTACTCTTCTCTAACATTTTTGAGGAAGTTTTGTCTAATT
ATCAATATTGAGGATCAGGGCTCCTAGGCTCAGTGGTAGCTCTGGCTTAGACACCACCTG
GAGTGATCACCTCTTGGGGACCTGCCTATCCCACTTCACAGGTGAGGCATGGCAATTCT
GGAAGCTGATTAAACACACATAAACCAAAACCAACAACAGGCCCTTGGGTGAAAGGTG
CTATATAATTGTGAAGTATTAAGCCTACCGTATTTTCAGCCATGATAAGAACAGAGTGCCT
GCATTCCCAGGAAAATACGAAAATCCCATGAGATAAATAAAAAATATAGGTGATGGGCAGA
TCTTTTCTTTAAATAAAAAAGCAAAAACCTCTTGTGGTACCTAGTCAGATGGTAGACGAG
CTGCTGCTGCCGAGGAGCACCTCTATACAGGACTTAGAAGTAGTATGTTATTCCTGGT
TAAGCAGGCATTGCTTTGCCCTGGAGCAGCTATTTTAAGCCATCTCAGATTCTGTCTAAA
GGGGTTTTTTGGGAAGACGTTTTCTTTATCGCCCTGAGAAGATCTACCCAGGGAGAATC
TGAGACATCTTGCCCTACTTTTTCTTATTAGCTTTCTCCTCATCCATTTCTTTATACCTT
TCCTTTTGGGGAGTTGTTATGCCATGATTTTTGGTATTTATGTAAAAGGATTATTACTA
ATTCTATTTCTCTATGTTTATTCTAGTTAAGGAAATGTTGAGGGCAAGCCACCAATTAC
CTAGGCTGAGGTTAGAGAGATTGGCCAGCAAAACTGTGGGAAGATGAACTTTGTCTATA
TGATTTTCATTATCACATGATTATAGAAGGCTGTCTTAGTGCAAAAACATACTTACATTT

FIGURE 123 Continued

CAGACATATCCAAAGGGAATACTCACATTTTGTTAAGAAGTTGAACTATGACTGGAGTAA
ACCATGTATTCCTTATCTTTTACTTTTTTCTGTGACATTTATGTCTCATGTAATTGC
ATTACTCTGGTGGATTGTTCTAGTACTGTATTGGGCTTCTTCGTTAATAGATTATTCAT
ATACTATAATTGTAAATATTTTGATACAAATGTTTATAACTCTAGGGATATAAAAACAGA
TTCTGATTCCTTCAAAAAAAAAA

FIGURE 124

```
></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA226874
><subunit 1 of 1, 157 aa, 1 stop
><MW: 17563, pI: 8.34, NX(S/T): 2
MLVLLAGIFVVHIATVIMLFVSTIANVWLVSN TVDASVGLWKNCTNISCSDSLSYASEDA
LKT VQAFMILSIIFCVIALLVFVFQ LFTMEKGNRFFLSGATTLCWLCILVG VSIYTSHY
ANRDGTQYHHGYSYILGWICFCFSFIIGVLYLVLRKK
```

FIGURE 125

GTCTGCGCGGAGTCTGAGCGGCGCTCGTCCCGTCCCAAGGCCGACGCCAGCACGCCGTCA
TGGCCCCCGCAGCGGCGACGGGGGGCAGCACCCCTGCCCAGTGGCTTCTCGGTCTTCACCA
CCTTGCCCGACTTGCTCTTCATCTTTGAGTTTATCTTCGGGGGCCTGGTGTGGATCCTGG
TGGCCTCCTCCCTGGTGGCCCTGGCCCTGGTCCAGGGCTGGGTGATGTTTCGTGTCTGTGT
TCTGCTTCGTGGCCACCACCACCTTGATCATCTGTACATAATTGGAGCCCACGGTGGAG
AGACTTCCTGGGTACCTTGACGCGAGCCTACCACTGCACCGCTGCCCTCTTTTACCTCA
GCGCCTCAGTCTGGAGGCCCTGGCCACCATCACGATGCAAGACGGCTTCACCTACAGGC
ACTACCATGAAAAACATTGCTGCCGTGGTGTCTCTCTACATAGCCACTCTGCTCTACGTGG
TCCATGCGGTGTTCTCTTTAATCAGATGGAAGTCTTCATAAAGCCGCAGTAGAACTTGAG
CTGAAAACCCAGATGGTGTAACTGGCCGCCCACTTTCCGGCATAACTTTTGTAGAAAAC
AGAAATGCCCTTGATGGTGGAAAAAGAAAAACAACCACCCCCCACTGCCCAAAAAAAAAA
AGCCCTGCCCTGTTGCTCGTGGGTGCTGTGTTTACTCTCCCGTGTGCCTTCGCGTCCGGG
TTGGGAGCTTGCTGTGTCTAACCTCCAACCTGCTGTGCTGTCTGCTAGGGTCACCTCCTGT
TTGTGAAAGGGGACCTTCTTGTTCGGGGGTGGGAAGTGGCGACCGTGACCTGAGAAGGAA
AGAAAGATCCTCTGCTGACCCCTGGAGCAGCTCTCGAGAACTACCTGTTGGTATTGTCCA
CAAGCTCTCCCGAGCGCCCCATCTTGTGCCATGTTTAAAGTCTTCATGGATGTTCTGCAT
GTCATGGGGACTAAAACTCACCCAACAGATCTTTCCAGAGGTCCATGGTGAAGACGATA
ACCCTGTGAAATACTTTATAAAATGTCTTAATGTTC

FIGURE 126

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></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA227033
><subunit 1 of 1, 153 aa, 1 stop
><MW: 16714, pI: 5.89, NX(S/T): 0
MAPAAATGGSTLPSGFSVFTTLPDLLFIFEFIGGLVWILVASSLVPWPLVQGWVMFVSV
FCFVATTTLIILYIIGAAGGETSWVTLDAAVHCTAALFYLSASVLEALATITMQDGFTYR
HYHENIAAVVFSYIATLLYVVHAVFSLIRWKSS
```


FIGURE 127

CCGCGGAAGTGGCAGGCGTTTCAGAGCGTCAGAGGCTGCGGATGAGCAGACTTGGAGGACTCCAGGCCAGAGAC
TAGGCTGGGCGAAGAGTCGAGCGTGAAGGGGGCTCCGGGCCAGGGTGACAGGAGGCGTGCTTGAGAGGAAGAAG
TTGACGGGAAGGCCAGTGCACGGCAAATCTCGTGAACCTTGGGGGACGAATGCTCAGGATGCGGGTCCCCGCC
CTCCTCGTCTCTCTTCTGCTTCAGAGGGAGAGCAGGCCCCGTCGCCCCATTTCTGCAACAGCCAGAGGACCT
GGTGGTGCTGCTGGGGGAGGAAGCCCCGGCTGCCGTGTGCTCTGGGCGCCTACTGGGGGCTAGTTCACTGGACTA
AGAGTGGG
CTGGCCCTAGGGGGCCAAAGGGACCTACCAGGGTGGTCCCGGTACTGGATATCAGGGAATGCAGCCAATGGCCA
GCATGACCTCCACATTAGGCCCCGTGGAGCTAGAGGATGAAGCATCATATGAATGTCAGGCTACACAAGCAGGCC
TCCGCTCCAGACCAGCCCACTGCACGTGCTGGTCCCCCAGAAGCCCCCAGGTGCTGGGCGGCCCCCTCTGTG
TCTCTGGTTGCTGGAGTTCTTGCGAACCTGACATGTGCGAGCCGTGGGGATGCCCGCCCTACCCCTGAATTGCT
GTGGTTCCGAGATGGGGTCTGTTGGATGGAGCCACCTTTCATCAGACCCTGCTGAAGGAAGGGACCCCTGGGT
CAGTGGAGAGCACCTTAACCCCTGACCCCTTTCAGCCATGATGATGGAGCCACCTTTGTCTGCGGGGCCCCGAGC
CAGGCCCTGCCACAGGAAGAGACACAGCTATCACACTGAGCCTGCAGTACCCCCAGAGGTGACTCTGTCTGTC
TTCGCCACACACTGTGCAGGAGGGAGAGAAGGTCATTTCTGTGCCAGGCCACAGCCCAGCCTCTGTCAAG
GCTACAGGTGGGCAAAAGGGGGCTCTCCGGTGCTCGGGGCCCCGCGGCCAAGGTTAGAGGTCTGTGCAGACGCC
TCGTTCTGACTGAGCCCCGTGCTCTGCGAGGTGAGCAACGCCGTGGGTAGCGCCAACCCGAGTACTGCGCTGGA
TGTGCTGTTTGGGCGGATTCTGCAGGCAAAGCCGGAGCCCGTGCTCCGTGGACGTGGGGGAAGACGCTTCCTTCA
GCTGCGCCTGGCGCGGAACCCGCTTCCACGGGTAACTGGACCCGCGCGGTGGCGCGCAGGTGCTGGGCTCT
GGAGCCCACTGCGTCTTCCGTGCGGTGGGGCCCCAGGACGCAGGCGACTATGTGTGCAGAGCTGAGGCTGGGCT
ATCGGGCTGCGGGGCGGCGCCGCGGAGGCTCGGCTGACTGTGAACGCTCCCCAGTAGTGACCGCCCTGCACT
CTGCGCCTGCCTTCTGAGGGGCCCTGCTCGCCTCCAGTGTCTGGTTTTCGCCTCTCCCGCCCCAGATGCCGTG
GTCTGGTCTTGGGATGAGGGCTTCTGAGGGCGGGGTCGAGGGCCGTTTCTGGTGGAGACATTCCTGCCCC
AGAGAGCCGCGGGGGACTGGGTCCGGGCCTGATCTCTGTGCTACACATTTGCGGGACCCAGGAGTCTGACTTTA
GCAGGAGCTTTAACTGCAGTGCCCGGAACCGGCTGGGCGAGGGAGGTGCCAGGCCAGCCTGGGCGCTAGAGAC
TTGTGCCCCACTGTGCGGATAGTGCCGGAGTGCCCGCTGCCACCACAACCTCTCCTTATGGTCATCACTGGGGT
GGCCCTCTGCTGCTGGCGCCACAGCAAGGCTCAGCCTCTTCTCCGAGCAAAAGAACCTGATGCGAATCCCTG
GCAGCAGCGACGGCTCCAGTTCACGAGGTCTGAAGAAGAGGAGACAGGCAGCCGCGAGGACCGGGGCCCCATT
GTGCACACTGACCACAGTGATCTGGTTCTGGAGGAGGAAGGGACTCTGGAGACCAAGGACCCAACCAACGGTTA
CTACAAGGTCCGAGGAGTCACTGTGAGCCTGAGCCTTGGCGAAGCCCTTGGAGGAGTCTCTTCTGCCACCAC
CCTCCCCCTTGGGCCCCCAGGGACCCCTACCTTCTATGACTTCAACCCACACCTGGGCATGGTCCCCCCTGC
AGACTTTACAGAGCCAGGGCAGGCTATCTCACCACACCCACCCCTCGAGCTTTCACCAGCTACATCAAACCCAC
ATCCTTTGGGCCCCCAGATCTGGCCCCCGGGACTCCCCCTTCCCATATGCTGCCTTCCCCACACCTAGCCACC
CGCGTCTCCAGACTCACGTGTGACATCTTCCAATGGAAGAGTCTGGGATCTCCAATTTGCCATAATGGATTG
TTCTGATTTCTGAGGAGCCAGGACAAGTTGGCGACCTTACTCCTCCAAAAGTGAACACAAGGGGAGGGAAAGAT
CATTACATTTGTGAGGAGCATTGTATACAGTCAGCTCAGCCAAAGGAGATGCCCCAAGTGGGAGCAACATGGC
CACCCAATATGCCACCTATTTCCCGGTGTAAAAGAGATTCAAGATGGCAGGTAGGCCCTTTGAGGAGAGATGG
GGACAGGGCAGTGGGTGTTGGGAGTTTGGGGCCGGATGGAAGTTGTTTCTAGCCACTGAAAGAAGATATTTCA
AGATGACCATCTGCATTGAGAGGAAAGGTAGCATAGGATAGATGAAGATGAAGAGCATACCAGGCCCCACCCCTG
GCTCTCCCTGAGGGGAACCTTGTCTCGGCCAATGGAAATGCAGCCAAGATGGCCATATACTCCCTAGGAACCCAA
AATGGCCACCATCTTGATTTTACTTTCTTAAAGACTCAGAAAGACTTGAGCCCAAGGAGTGGGGATACAGTGA
GAATTACCACTGTTGGGGCAAAATATTGGGATAAAATATTTATGTTTAAATAAAAAAAGTCAAAGAGAAA
AAAAA

FIGURE 128

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA145841

><subunit 1 of 1, 708 aa, 1 stop

><MW: 75093, pI: 6.65, NX(S/T): 3

MLRMRVPALLVLLFCFRGRAGPSPHFLQQPEDLVVLLGEEARLPCALGAYWGLVQWTKSG
LALGGQRDLPGWSRYWISGNAANGQHDLHIRPVELEDEASYECQATQAGLRSRPAQLHVL
VPPEAPQVLGGPSVSLVAGVPANLTCSRSGDARPTPELLWFRDGVLLDGATFHQTLLKEG
TPGSVESTLTLPFSHDDGATFVCRARSQALPTGRDTAITLSLQYPPEVTLSASPHTVQE
GEKVIFLCQATAQPPVTGYRWAKGGSPVLGARGPRLEVVDASFLTEPVSCEVSNVAVGSA
NRSTALDVLFGPILQAKPEFVSVDVGEDASFSCAWRGNPLPRVTWTRRGAQVLGSGATL
RLPSVGPEDAGDYVCRAEAGLSGLRGGAEEARLTVNAPPVVTAHSAFAFLRGPAPLQCL
VFASPAPDAVVWSWDEGFLEAGSQGRFLVETFPAPESRGGLGPGGLISVLHISGTQESDFS
RSFNCSARNRLGEGGAQASLGRDLLPTVRIVAGVAAATTTLLMVITGVALCCWRHASKAS
ASFSEQNLMRIPGSSDGSSSRGPEEEETGSREDRGPVHTDHSDLVLEEEGTLETKDPT
NGYYKVRGVSVSLSLGEAPGGGLFLPPPSPLGPPGTPTFYDFNPHLMVPPCRLYRARAG
YLTPHPRAFTSYIKPTSFPGPDLAGTFFFYAAFPPTPSHPRLQTHV

Important features of the protein:

Signal peptide:

Amino acids 1-20

Transmembrane domain:

Amino acids 511-531

N-glycosylation sites:

Amino acids 143-147;301-305;484-488

N-myristoylation sites:

Amino acids 48-54;60-66;79-85;139-145;180-186;183-189;355-361;383-389;
387-393;460-466;473-479;494-500;495-501;514-520;528-534;
554-560;592-598;608-614

Amidation site:

Amino acids 500-504

Cell attachment sequence:

Amino acids 149-152

Multicopper oxidases signature 1:

Amino acids 445-466

Immunoglobulin domain:

Amino acids 326-377

FIGURE 129

GGACCACAGCTCCTCCCGTGCATCCACTCGGCCTGGGAGGTTCTGGATTTTGGCTGTGCA
GGGAGTTTGCCTGCCTCTCCAGAGAAAGATGGTTCATGAGGCCCTGTGGAGTCTGCTTCT
CTGGGAAGCCCTACTTCCCATTAACAGTTACTGGTGGCCAAAGTGCTGAGCAAAGTCGGGG
CTCGGTGCTGCTGGTGGCAGCGCGTCCCGCTGGCTTCCAAGTCCGTGAGGCTATCTGGCG
ATCTCTCTGGCCTTCAAGAGCTCCTGGCCACGTTTTTCCGAGGCTCCCTGGAGACTCT
GTACCATTCCCGCTTCTGGGCCGAGCCAGCTACACAGCAACCTCAGCCTGGAGCTCGG
GCCGCTGGAGTCTGGAGACAGCGGCAACTTCTCCGTGTTGATGGTGGACACAAGGGGCCA
GCCCTGGACCCAGACCTCCAGCTCAAGGTGTACGATGCAGTGCCAGGCCCGTGGTACA
AGTGTTCATTGCTGTAGAAAGGGATGCTCAGCCCTCCAAGACCTGCCAGGTTTTCTGTCT
CTGTTGGGCCCCCAACATCAGCGAAATAACCTATAGCTGGCGACGGGAGACAACCATGGA
CTTTGGTATGGAACCACACAGCCTCTTACAGACGGACAGGTGCTGAGCATTTCCTGGG
ACCAGGAGACAGAGATGTGGCCTATTCTGTCATTGTCTCCAACCTGTGAGCTGGGACTT
GGCCACAGTACGCCCCCTGGGATAGCTGTATCATGAGGCAGCACCCAGGGAAGGCCCTCTA
CAAAGATGTGCTGCTGGTGGTGGTGCCTGTCTCGCTGCTCCTGATGCTGGTTACTCTCTT
CTCTGCTGGCACTGGTGGCCCTGCTCAGGGAAAAAGAAAAGGATGTCATGCTGACAG
AGTGGGTCCAGAGACAGAGAACCCCTTGTGCAGGATCTGCCATAAAGGACAATATGAAC
TGATGCCTGGACTATCAGTAACCCCACTGCACAGGCACACGATGCTCTGGGACATAACTG
GTGCCTGGAAATCACCATGGTCCCTCATATCTCCATGGGAATCCTGTCTGCTCGCCTCGAAG
AGCAGCCTGGGCGAGCCATCACACCAGGAGCAGGAAGCACCAGCACGTTTACACCTCC
CCCTTCCCTCTCCCATCTTCTCATATCCTGGCTCTTCTCTGGGCAAGATGAGCCAAGCAG
AACATTCCATCCAGGACACTGGAAGTTCTCCAGGATCCAGATCCATGGGGACATTAATAG
TCCAAGGCATTCCCTCCCCACCACTATTCTATAAAGTATTAACCAACTGGCACCAAGGAA
TTGCCCTCAGCTGAGTCTTAGGCTCTAAAGATATTACATATTTGAACTAATAGAGGAA
CTCTGAGTCAACCATGCCAGCATCAGCTTCAGCCCCAGACCCTGCAGTTTGAGATCTGAT
GCTTCTCTGAGGGCCAAGGCATTGCTGTAGAAAAGGCTAGAAAATAGGTGAAAAGTGAGAG
GTGGGGGACAGGGGTTTCTTTCTGGCCTAAGGACTTTCAGGTAATCAGAGTTCATGGG
CCCTCAAAGGTAAATTGCAGTTGTAGACACCGAGGATGGTTGACAACCCATGGTTGAGAT
GGGCACCGTTTTGCAGGAACACCATATTAATAGACATCCTCACCATCTCCATCCGCTCT
CAGCCTCCTGAGGATCTGGGAGTGAGGGTGGAGAGTCTTTCTCAGCTCCAGCACAG
TGGCCAGGAAAAGAAATACTGAATTTGCCCCAGCCAACAGGACGTTCTTGACAACTTCA
AGAAAAGCAGCTCAGCTCAGGATGAGTCTTCTGCTGAACTGAGAGAGTGAAGAACCA
TAAAACGCTATGCAGAAGGAACATTATGGAGAGAAAGGTAAGGCACTCTAGAATCT
GCCACATTCAATTTCAAATGCAAATGCAGAAGACTTACCTTAGTTCAAGGGGAGGGGACA
AAGACCCACAGCCCCAACAGCAGGACTGTAGAGGTCACTCTGACTCCATCAAACCTTTTA
TTGTGGCCATCTTAGGAAAATACATTCTGCCCTGAATGATTCTGTCTAGAAAAGCTCTG
GAGTATTGATCACTACTGGAAAAACACTTAAGGAGCTAAACTTACCTTCGGGGATTATTA
GCTGATAAGGTTACAGTTTCTCTCAGCCAGGTGTAAGTGGATTTTTTCTGGGGCCTCAA
TCCAGTCTTGATAACAGCGAGGAAAGAGGTATTGAAGAAAAGGGGTGGGTTTGAAGTAC
TATTTTCCCGAGGGTGGCTTCAATCTCCCCACCTAGGATGTGAGCCCTGTCCAAGGACCT
TCCCTCTTCTCCCCCAGTTCCCTGGGCAATCACTTCACTTGGACAAAGGATCAGCACAG
CTGGCCCTCCAGATCCACATCACCCTCTTCCACTCGATTGTTCCAGATCCTCCCTGCCT
GGCCTGCTCAGAGGTTCCCTGTTGGTAACCTGGCTTTATCAAATTCTCATCCCTTTCCCA
CACCCACTTCTCTCTATCACTTCCCCCAAGATTACCTGAACAGGGTCCATGGCCACTC
AACCTGTCAGCTTGCACCATCCCCACCTGCCACCTACAGTCAGGCCACATGCCTGGTCAC
TGAATCATGCAAAACTGGCCTCAGTCCCTAAAAATGATGTGGAAAGGAAAGCCAGGATC
TGACAATGAGCCCTGGTGGATTGTGGGGAAAAATACACAGCACTCCCCACCTTTCTTT
CGTTCATCTCAGGGCCCCACCTCAGATCAAAGCAGCTCTGGATGAGATGGGACCTGCAG
CTCTCCCTCCCAAGGTGACTCTTAGCAACCTCATTTGACAGTGGTTGTAGCGTGGTG
CACCAGGGCCTTGTGAACAGATCCACACTGCTCTAATAAAGTTCCCATCCTTAATGACT
CACTTGTCACTAGTGGACTAATTAACCTCCACCAAAAAACAAAGTGCTTCTGTGA
GACCAATTTTGTGCTAATGAGCATTGAGACTGATGCTTGTAGTCACACCACAACAAAT
ATTGATTGAGGGCGCTGCATGTGCTGGGTACATTTCTTGGCACTGGGAATCAGTAGTCA
AGCGAAACCTTGCCTTTGAGAGTTTATGGTCTGGATAATATAAATAAACAAGTAAGCAT
AAAAAAAAAAAAAAAA

FIGURE 130

```
><Wed Dec 6 14:16:26 2000 DNA188342 [min]
></usr/seqdb2/sst/DNA/Dnaseqs:min/ss.DNA188342
><subunit 1 of 1, 285 aa, 1 stop
><MW: 31670, pI: 6.12, NX(S/T): 3
MVMRPLWSLLLWEALLPITVTGAQVLSKVGGSVLLVAARPPGFQVREAIWRS LWPSEELL
ATFFRGSLETLYHSRFLGRAQLHSNLSLELGPLESGDSGNFSVLMVDTRGQPWTQTLQLK
VYDAVPRPVVQVFIAVERDAQPSKTCQVFLSCWAPNISEITYSWRRETMTDFGMEPHSLF
TDGQVLSISLGPGRDVAYS CIVSNPVSWDLATVTPWDSCHHEAAPGKASYKDVLLVVVP
VSLLLMLVTLFSAWHWCPCSGKKKKDVHADRVGPETENPLVQDLP
```

FIGURE 131

GGGAAGCCATGGAGCCGCGGGCGCTCGTCACGGCGCTCAGCCTCGGCCTCAGCCTGTGCTCCCTGGGGCTGCTC
GTCACGGCCATCTTCACCGACCACTGGTACGAGACCGACCCCGCGCCACAAGGAGAGCTGCGAGCGCAGCCG
CGCGGGCGCCGACCCCGGACCAGAAGAACCGCCTGATGCCGCTGTGCGACCTACTCGGGCCTCTGGAGGAAG
TGCTACTTCCTGGGCATCGACCGGGACATCGACACCCTCATCCTGAAAGGTATTGCGCAGCGATGCACGGCCAT
CAAGTACCACTTTTCTCAGCCCATCCGCTTGCGAAACATTCTTTTAATTTAACCAAGACCATAACAGCAAGATG
AGTGGCACCTGCTTCGGATATTTTGCACCATTTCCTCTGTACTTATGCCGCCAGTATCTCGTATGATTTGAAC
CGGCTCCCAAAGCTAATTTATAGCCTGCCTGCTGATGTGGAACATGGTTACAGCTGGTCCATCTTTTGCGCCTG
GTGCAGTTTAGGCTTTTATTGTGGCAGCTGGAGGTCTCTGCATCGCTTATCCGTTTATTAGCCGGACCAAGATTG
CACAGCTAAAGTCTGGCAGAGACTCCACGGTATGACTGTCCTCACTGGGCCTGTCCAAGCACAAAGCGGTCTTT
TACATTCCAACCTGTTGCCTGCCAGCCCTTTCTGGATTACTGATAGAAAATCATGCAAACCTCCCAACCTTTC
TAAGGACAAGACTACTGTGGATTCAAGTGCTTTAATGACTATTTATGCGTTGACTGTGAGAATAGGGAGCAGTG
CCATGGGACATTTCTAGGTGTAGAGAAAGAAGAACTGCAATGGAAAAATTTGTATGATTTCCATTTATTTTCA
AAAGTTTGATGTAACAATTACCCGAGAGTCATTTCTACTTGCAAAAGGATTCGTAACAAAGCGAGTATAATTT
TCTTGTCATTGTATCATGCTTGTTAAATTTAATGCAGCATCTTCAGAACTTGTCCTGATGGTGTCTTATTGTG
TCAGACCAAATATTTGTGCATTATTTGTGGACGTTCTTGTACAGGAAGATTCTTCTTCTGTTGCCTTATTG
TTTTTTTTTTTTTTTAACTCTCTTCTGTCTTTGTACTGGAATCGAAATCATAAGATAAACAGATCAAACGT
GCTTAAGAGCTAACTCGTGACACTATGCAGTATTGTTTGAAGACCTGTTGTTCAACCTCTGTCTCTTTATGTTA
ATGGATTTCTGCATTAAATGACTGCCCCC

FIGURE 132

MEPRALVTALSLGLSLCSLGLLVTAIFTDHWYETDPRRHKESCERSRAGADPPDQKNRLM
PLSHLLGPLLEEVLLPGHRPGHRHPPHRYCAAMHGHQVPLFSAHPLAKHSF

Important features of the protein:

Signal peptide:

1-17

N-myristoylation site.

13-19

20-26

FIGURE 133

CAAAGCGGCGGCTGTCCGCGGTGCCGGCTGGGGGCGGAGAGGCGGCGGTGGGCTCCCTGGG
GTGTGTGAGCCCGGTGATGGAGCCGGGCCCCGACAGCCGCGCAGCGGAGGTGTTGTTGCCG
CCGTGGCTGCCGCTGGGGCTGCTGCTGTGGTGGGGCTGGCCCTGGGCGCGCTCCCCCTCG
GCAGCAGTCCGCACAGGGTCTTCCACGACCTCCTGTGCGAGCAGCAGTTGCTGGAGGTGGA
GGACTTGTCCCTGTCCCTCCTGCAGGGTGGAGGGCTGGGGCCTCTGTGCTGCCCCCGGAC
CTGCCGGATCTGGATCCTGAGTGCCGGGAGCTCCTGCTGGACTTCGCCAACAGCAGCGCAG
AGCTGACAGGGTGTCTGGTGCGCAGCGCCCGGCCCCGTGCGCCTCTGTGACACCTGCTACCC
CCTCTTCCAACAGGTCGTGAGCAAGATGGACAACATCAGCCGAGCCGCGGGAATACTTCA
GAGAGTCAGAGTTGTGCCAGAAGTCTCTTAATGGCAGATAGAATGCAAATAGTTGTGATTCT
TCTCAGAATTTTTTAATACCACATGGCAGGAGGCAAATTGTGCAAATTGTTTAAACAAACAA
CAGTGAAGAATTATCAAACAGCACAGTATATTTCTTAATCTATTTAATCACACCCTGACC
TGCTTTGAACATAACCTTCAGGGGAATGCACATAGTCTTTTACAGACAAAAAATTATTCAG
AAGTATGCAAAAACTGCCGTGAAGCATACAAACTCTGAGTAGTCTGTACAGTGAAATGCA
AAAAATGAATGAACTTGAGAATAAGGCTGAACCTGGAACACATTTATGCATTGATGTGGAA
GATGCAATGAACATCACTCGAAAACTATGGAGTCGAACCTTTCAACTGTTGAGTCCCTTGCA
GTGACACAGTGCCCTGTAATTGCTGTTTCTGTGTTTCACTCTCTTTCTACCTGTTGTCTTCTA
CCTTAGTAGCTTTCTTCACTCAGAGCAAAAGAAACGCAAACTCATTCTGCCCAAACGTCTC
AAGTCCAGTACCAGTTTTGCAAATATTCAGGAAAATTCAAACTGAGACCTACAAAATGGAG
AATTGACATATCACGTGAATGAATGGTGGAAGACACAACCTTGGTTTCAGAAAGAAGATAAA
CTGTGATTTGACAAGTCAAGCTCTTAAGAAATACAAGGACTTCAGATCCATTTTTAAATAA
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CCAG

FIGURE 134

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><subunit 1 of 1, 334 aa, 1 stop
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QVVSMDNISRAAGNTSESQSCARSLLMADRMQIVVILSEFFNTTWQEQANCANCLTNSE
ELSNSTVYFLNLFNHTLTCTFEHNLQGNHSLQLTKNYSEVCKNCREAYKTLSSLYSEMOK
MNELENKAEPGTHLCIDVEDAMNITRKLWSRTFNCSVPCSDTVPVIAVSVFILFLPVVY
LSSFLHSEQKKRKLILPKRLKSSTSFANIQENSN
```

Important features of the protein:

Signal peptide:

Amino acids 1-31

Transmembrane domain:

Amino acids 278-300

N-glycosylation sites:

Amino acids 93-97;128-132;135-139;163-167;177-181;
184-188;194-198;216-220;263-267;274-278

cAMP- and cGMP-dependent protein kinase phosphorylation site:

Amino acids 10-14

N-myristoylation sites:

Amino acids 27-33;206-212;251-257

Leucine zipper pattern:

Amino acids 190-212

FIGURE 135

GCCAGGCCCTATCTCCCTGCCAGGAGGCCGAGTGGGGGAGGTGACAGCGGGCGGTTGGAGGGGGAGGGATGCC
ACGCGCTTCTGCCTCAGGTGTTCTGCGTTGTTTGTGTCAGTGGAGAGCAGGGAGTGGGGCCAGCCAGCAGAAACA
GTGGGCTGTACAACATCACCTTCAAATATGACAATTGTACCACCTACTTGAATCCAGTGGGGAAGCATGTGATT
GCTGACGCCCAGAATATCACCATCAGCCAGTATGCTTGCCATGACCAAGTGGCAGTCACCATTCTTTGGTCCCC
AGGGGCCCTCGGCATCGAATTCCCTGAAAGGATTTCCGGTAATACTGGAGGAGCTGAAGTCGGAGGGAAGACAGT
GCCAACAACTGATTCTAAAGGATCCGAAGCAGCTCAACAGTAGCTTCAAAGAAGTGAATGGAATCTCAACCT
TTCCTGAATATGAAATTTGAAACGGATTATTTTCGTAAAGGTTGTCCCTTTTCCCTCCATTAAAAACGAAAGCAA
TTACCACCCCTTCTTCTTTAGAACCCGAGCCTGTGACCTGTTGTTACAGCCGGACAATCTAGCTTGTAAACCT
TCTGGAAGCCTCGGAACCTGAACATCAGCCAGCATGGCTCGGACATGCAGGTGTCCTTCGACCACGCACCGCAT
GGCTCGGACATGCAGGTGTCCTTCGACCACGCACCGCACAACCTTCGGCTTCCGTTTCTTCTATCTTCACTACAA
GCTCAAGCACGAAGGACCTTCAAGCGAAAGACCTGTAAGCAGGAGCAAACTACAGAGATGACCAGCTGCCTCC
TTCAAATGTTTCTCAGGGGATTATATAATTGAGCTGGTGGATGACACTAACACAACAAGAAAAGTGATGCAT
TATGCCTTAAAGCCAGTGCACTCCCGTGGGCGGGGCCCATCAGAGCCGTGGCCATCAGAGTCCCACTGGTAGT
CATATCGGCATTCGCGACGCTCTTCACTGTGATGTGCCGAAGAAGCAACAAGAAAATATATATTACATTTAG
ATGAAGAGAGCTCTGAGTCTTCCACATACACTGCAGCACTCCAAGAGAGAGGCTCCGGCCGCGGCCGAAGGTC
TTTCTCTGCTATTCCAGTAAAGATGGCCAGAATCACATGAATGTCGTCCAGTGTTCGCGCTACTTCTCCAGGA
CTTCTGTGGCTGTGAGGTGGCTCTGGACCTGTGGGAAGACTTCAGCCTCTGTAGAGAAGGGCAGAGAGAATGGG
TCATCCAGAAGATCCACGAGTCCCAGTTCATCATTGTGGTTTGTTCCAAAGGTATGAAGTACTTTGTGGACAAG
AAGAACTACAAACACAAAGGAGGTGGCCGAGGCTCGGGGAAAGGAGAGCTCTTCCCTGGTGGCGGTGTCAGCCAT
TGCCGAAAAGCTCCGCCAGGCCAAGCAGAGTTTCGTCCGCGGCGCTCAGCAAGTTTATCGCCGTCTACTTTGATT
ATTCTGCGAGGGAGACGTCCCCGGTATCCTAGACCTGAGTACCAAGTACAGACTCATGGACAATCTTCCTCAG
CTCTGTTCCACCTGCACTCCCGAGACCACGGCCTCCAGGAGCCGGGGCAGCACACGCGACAGGGCAGCAGAAG
GAACTACTTCCGGAGCAAGTCAGGCCGGTCCCTATACGTGCGCATTTGCAACATGCACCAGTTTATTGACGAGG
AGCCCGACTGGTTCGAAAAGCAGTTCGTTCCCTTCCATCCTCCTCCACTGCGCTACCGGGAGCCAGTCTTGAG
AAATTTGATTGCGGCTTGTTTAAATGATGTGATGTGCAAAACAGGGCCTGAGAGTGACTTCTGCCTAAAGGT
AGAGGCGGCTGTTCTTGGGGCAACCGGACCAGCCGACTCCAGCACGAGAGTCAAGCATGGGGGCTGGACCAAG
ACGGGGAGGCCCGGCTGCCCTTGACGGTAGCGCCGCCCTGCAACCCCTGCTGCACACGGTGAAAGCCGGCAGC
CCCTCGGACATGCCGCGGACTCAGGCATCTATGACTCGTCTGTGCCCTCATCCGAGCTGTCTTGCCACTGAT
GGAAGGACTCTCGACGGACCAGACAGAAACGTCTTCCCTGACGGAGAGCGTGTCTCTCTTCAGGCCTGGGTG
AGGAGGAACCTCCTGCCCTTCTTCCAAGTCCTCTCTTCTGGGTGATGCAAGCAGATCTTGGTTGCCGAGC
TACACTGATGAACTCCACGCGGTGCGCCCTTTGTAACAAAACGAAAGAGTCTAAGCATTGCCACTTTAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 136

MPRASASGVPALFVSQEQVGPASRNSGLYNITFKYDNCTTYLNPVGKHVIADAQNITISQYACHDQVAVTILW
SPGALGIEFLKGFRVILEELKSEGRQCQQLILKDPKQLNSSFKRTGMESQPFLNMKFETDYFVKVVPFPSIKNE
SNYHPFFFRTRACDLLLQPDNLACKPFWKPRNLNISQHGSDMQVSFDHAPHGSDMQVSFDHAPHNFGFRFFYLH
YKLKHEGPFKRTCKQEQTTEMTSCLLQNVSPGDYIIELVDDTNTTRKVMHYALKPVHSPWAGPIRAVAITVPL
VVISAFATLFTVMCRKKQQENIYSHLDEESSESSTYTAALPRERLRPRPKVFLCYSSKDGQNHMNVVQCFAYFL
QDFCGCEVALDLWEDFSLCREGQREWVIQKIHESQFIIVVCSKGMKYFVDKKNYKHKGGRGSGKGELFLVAVS
AIAEKLQAKQSSSAALSKEFIQVYFDYSCEGDVPGILDSTKYRLMDNLPQLCSHLHSRDHGLQEPGQHTRQGS
RRNYFRSKSGRSLYVAICNMHQFIDEEDWFQKQVFPFHPPLRYREFVLEKFDGSLVLDVMCKPGPESDFCL
KVEAAVLGATGPADSQHESQHGGLDQDGEARPALDGSAAQLPLLHTVKAGSPSDMPRDSGIYDSSVPSSLSLP
LMEGLSTDQTETSSLTESVSSSSGLGEEPPALPSKLLSSGSCKADLGCRSYTDELHAVAPL

Transmembrane domain:

Amino acids 283-307

N-glycosylation sites:

Amino acids 31-34;38-41;56-59;
113-116;147-150;182-185;266-269

Glycosaminoglycan attachment sites: Amino acids 433-436;689-692

cAMP- and cGMP-dependent protein kinase phosphorylation:

Amino acids 232-235

Tyrosine kinase phosphorylation sites: Amino acids 312-319;416-424

N-myristoylation site:

Amino acids 19-24;375-380;428-433;
429-434;432-437;517-522;574-579;
652-657;707-712

FIGURE 137

CAACTGCACCTCGGTTCTATCGATAGCCACCAGCGCAACATGACAGTGAAGACCCTGCATGGCCCAGCCATGGT
CAAGTACTTGCTGCTGTCGATATTGGGGCTTGCCCTTCTGAGTGAGGCGGCAGCTCGGAAAATCCCCAAAGTAG
GACATACTTTTTTCCAAAAGCCTGAGAGTTGCCCGCCTGTGCCAGGAGGTAGTATGAAGCTTGACATTGGCATC
ATCAATGAAAACCAGCGCGTTTCCATGTCACGTAACATCGAGAGCCGCTCCACCTCCCCCTGGAATTACACTGT
CACTTGGGACCCCAACCGGTACCCCTCGGAAGTTGTACAGGCCCAGTGTAGGAACCTGGGCTGCATCAATGCTC
AAGGAAAGGAAGACATCTCCATGAATTCCGTTCCCATCCAGCAAGAGACCCTGGTCGTCCGGAGGAAGCACCAA
GGCTGCTCTGTTTCTTTCCAGTTGGAGAAGGTGCTGGTGACTGTTGGCTGCACCTGCGTCACCCCTGTCATCCA
CCATGTGCAGTAAGAGGTGCATATCCACTCAGCTGAAGAAG

FIGURE 138

MTVKTLHGPMVKYLLLSILGLAFLSEAAARKIPKVGHTFFQKPESCPPVPGGSMKLDIGIINENQRVMSRNI
ESRSTSPWNYTVTWDPNRYPSEVVQAQCRNLGCINAQGKEDISMNSVPIQETLVVRRKHQGCSVSFQLEKVLV
TVGCTCVTPVIHHVQ

Signal sequence:

Amino acids 1-30

N-glycosylation site:

Amino acids 83-86

N-myristoylation sites:

Amino acids 106-111;136-141

FIGURE 139

TTCTGCTATAGAGATGGAACAGTATATGGAAAGCTCCCAAGAAAGTGAAGAGAGGAAATT
GGAAATTTGTGAGTGGACCTTCTGATACTGCTCCTCCTTGCCTGGAAAAGGGGAAAGAAC
TGCATGCATATTATTTCAGCGTCCTATATTCAAAGGATATTCTTGGTGATCTTGGAAGTGT
CCGTATCATGGAATCAATCTCTATGATGGGAAGCCCTAAGAGCCTTAGTGAAACTTGTTT
ACCTAATGGCATAAATGGTATCAAAGATGCAAGGAAGGTCACTGTAGGTGTGATTGGAAG
TGGAGATTTTGCCAAATCCTTGACCATTGCACTTATTAGATGCGGCTATCATGTGGTCAT
AGGAAGTAGAAATCCTAAGTTTGCTTCTGAATTTTTTCTCATGTGGTAGATGTCACTCA
TCATGAAGATGCTCTCACAAAAACAAATATAATATTGTTGCTATACACAGAGAACATTA
TACCTCCCTGTGGGACCTGAGACATCTGCTTGTGGGTAAAATCCTGATTGATGTGAGCAA
TAACATGAGGATAAACCAGTACCCAGAATCCAATGCTGAATATTGGCTTCATTATTCCC
AGATTCTTTGATTGTCAAAGGATTTAATGTTGTCTCAGCTTGGGCACTTCAGTTAGGACC
TAAGGATGCCAGCCGGCAGGTTTATATATGCAGCAACAATATTCAAGCGGACAAACAGGT
TATTGAACCTTGCCCGCCAGTTGAATTTCAATCCCATTGACTTGGGATCCTTATCATCAGC
CAGAGAGATTGAAATTTACCCCTACGACTCTTTACTCTCTGGAGAGGGCCAGTGGTGGT
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ATATGCTAGAAACCAACAGAGTGACTTTTACAAAATTCCTATAGAGATTGTGAATAAAAC
CTTACCTATAGTTGCCATTACTTTGCTCTCCCTAGTATACCTTGCAGGTCTTCTGGCAGC
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GTTACAGTGTAGAAAACAGCTTGGATTACTAAGTTTTTTCTTCGCTATGGTCCATGTTGC
CTACAGCCTCTGCTTACCGATGAGAAGGTCAGAGAGATATTTGTTTCTCAACATGGCTTA
TCAGCAGGTTTCATGCAAATATTGAAAACCTTTGGAATGAGGAAGAAGTTTGGAGAATTGA
AATGTATATCTCCTTTGGCATAATGAGCCTTGGCTTACTTTCCCTCCTGGCAGTCACTTC
TATCCCTTCAGTGAGCAATGCTTTAAACTGGAGAGAATTCAGTTTTATTTCAGTCTACACT
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TTTTGAGGAAGAGTACTACAGATTTTATACACCACCAAACCTTTGTTCTTGCTCTTGTTTT
GCCCTCAATTGTAATTCTGGATCTTTTGCAGCTTTGCAGATACCCAGACTGAGCTGGAAC
TGGAATTTGTCTTCTTATGACTCTACTTCTTTAAAAGCGGCTGCCCATTCATTCTCTCA
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CAAAGGAAGGCAGCATGTGTCTTTTTTTCATCCCTTCATCTTGCTGCTGGGATTGTGGATA
TAACAGGAGCCCTGGCAGCTGTCTCCAGAGGATCAAAGCCACACCCAAAGAGTAAGGCAG
ATTAGAGACCAGAAAGACCTTGACTACTTCCCTACTTCCACTGCTTTTCTCTGCATTTAA
GCCATTGTAAATCTGGGTGTGTTACATGAAGTGAAATTAATTCTTTCTGCCCTTCAGTT
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TGAAAGCTTTTAAAGGATAATGTGCAATTCACATTAAATTTGATTTTCCATTGTCAATTA
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GCTATCAAATTACACACCATGTTTTCTATCATTCTCATAGATCTGCCTTATAAACATTTA
AATAAAAAGTACTATTTAATGATTTAACTTCTGTTTTGAAAAAAAAAAAAAAAAAAAAA
AAA

FIGURE 140

MESISMMGSPKSLSETCLPNGINGIKDARKVTVGVIGSGDFAKSLTIRLIRCGYHVVIGS
RNPKFASEFFPHVVDVTHHEDALTKTNIIFVAIHREHYTSLWDLRHLLVGKILIDVSNM
RINQYPESNAEYLASLFPDSLIVKGFNVVSAWALQLGPKDASRQVYICSNNIQARQQVIE
LARQLNFIPIDLGSLSSAREIENLPLRLFTLWRGPVVVAISLATFFFLYSFVRDVIHPYA
RNQQSDFYKIPIEIVNKTLPPIVAITLLSLVYLAGLLAAAYQLYGYTKYRRFPPWLETWLQ
CRKQLGLLSFFFAMVHVAYSCLCPMRRSERYLFLNMAYQQVHANIENSWNEEEVWRIEMY
ISFGIMSLGLLSLLAVTSIPSVSNALNWREFSFIQSTLGYVALLISTFHVLIYGWKRAFE
EEYRFFYTPPNFVLALVLPISIVILDLLQLCRYPD

Transmembrane domain:

210-230

256-278

360-382

391-412

430-450

N-glycosylation site.

256-259

cAMP- and cGMP-dependent protein kinase phosphorylation site.

29-32

Tyrosine kinase phosphorylation site.

416-424

N-myristoylation site.

8-13

24-29

34-39

193-198

274-279

FIGURE 141

CAGAGCCCTGCGGGAGGACTCAGAGTCAGGGACACAGCAGCGTCCGGCGAGATGAAGGCG
CTTGGGGCTGTCTGCTTGCCCTCTTGCTGTGCGGGCGGCCAGGGAGAGGGCAGACACAG
CAGGAGGAAGAGGAAGAGGACGAGGACCACGGGCCAGATGACTACGACGAGGAAGATGAG
GATGAGGTGGAAGAGGAGGAGACCAACAGGCTCCCTGGTGGCAGGAGCAGAGTGCTGCTG
CGGTGCTACACCTGCAAGTCCCTGCCCAGGGACGAGCGCTGCAACCTGACGCAGAACTGC
TCACATGGCCAGACCTGCACAACCCCTATTGCCCACGGGAACACCGAGTCAGGCCTCCTG
ACCACCCACTCCACGTGGTGCACAGACAGCTGCCAGCCCATCACCAAGACGGTGGAGGGG
ACCCAGGTGACCATGACCTGCTGCCAGTCCAGCCTGTGCAATGTCCACCCCTGGCAAAGC
TCCCCGAGTCCAGGACCCAACAGGCAAGGGGGCAGGCGGCCCCCGGGGCAGCTCCGAAACT
GTGGGCGCAGCCCTCCTGCTCAACCTCCTTGCCGGCCTTGAGCAATGGGGGCCAGGAGA
CCCTGACCCACGGCCCCCTCCCCACCCCCACCCGGCTCACCCCGGCCCTGCCAGCACTCT
GTCTGCTACCTTCCCCCTCCTGCCCCCTGCACCAGCTTTGGAGAATGGATTGAGTGCTCTT
GGGCGATCCAGCCAGCGCAGGCCCCCGGCCCGGTTGCTTCTCAGTTCCCGGCTGTGTC
CTTGGTGTCTTTCTCCACCACCTGTGAGCAGCAAGACTGCCGCACGTGGGCGCTGGGTC
CAGACCTCGGCTGCCACGTCCCAGGACCTGCAGCCCTCACGGGGGCTGGGGATCCCCATC
AGCACAGCCAGGCAGAGATGATACCCACCACACACCTGGGGGCCCCACACCCAGTCCCTC
ACCCTTAACTTCTGCCATGGGAATTTCTCCATCTGCAGCAGTCACACGGGCCCCACCTGC
CCTTCCCCAGGTGCGCCTCTCCGCTGTCTGGAGGGAAGGGGATTTGGAGGGAGGCTGTGCG
TCGCCCCCAGGAAAGACGGGCTGGGGGAGGCGGGACAGTGGGAGAGGCGCGCTGAGGAT
GAGAGGGCACAGGGAGGTGGGTGGGGTGAGGCCACATGCGGAGGGGCGGGGCGGGCGG
GGCTGGGGGACAGGCACCAAGTATGAAGAGGATGGGGCCAGCGGGCCTGTCTGGCTGT
GGCGTGAGCACCGCTATGGGAGACCTGCTTGAAAGTGAACTTGCAACCTTGATGGGG
AAGGGCCAGATGCTGGGTGGGTGCCTGTACCTTGAGGTGACCATCTAGGGTCAGTACCT
GCTGGGCTTAGGACAGCGCTGAGGCTGGGAATACCTGTCTCTGCTCTAGCAGAGGCTAA
AGCAGGCTAGAGCAGTGGAGGGGTGGAGTTGATGAAAGGAGAGGAGTAGATGAGATGGAA
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GGGTGTCTGATGGATCTGGGGGTGTGACAGAGGCTACCCTGTGCCAGGGAGGGGCGAG
AATGGGCTGCAGCTTCTGTCAGAGGAAGCAGGACTGGGTAGCAGAGCCGGGAAGGTGGG
TGCCCCATTACAGGGGGTCCCCAGGGTGTCTGTCAGGGCTGTGACTGCTGCAAGCT
CTGCCTTACCAGTAGCTGGTGCCAGGACAGAGCTCTGGGACAGCAGGAGAGGCCGAGC
CTGGGCCACAGCTCAGCCACTGACTTGGGTATCAGTTTCCCTTCTGAGAAGTACAGAGT
GAGACTTAAAGAACCCCTAGATCCCCACCAAGTTCAACACTCCATTAACTGGGAAGCCCAG
AGTCTGTCCGGCCTGCCAAGTTTCATCTGGTGGACAGCGGGAGGCCTCCGCTAACTGTT
CTCTTCTTTCTTATTAATAAAACACACAATGCCTAGCTGGGGGGTCGGAAGGCATAATG
CCCTAGATGGTGGGGTCACGTCTTTCTCCTTCTCCTTCTGCTGGCTGAAGTGA
TGACTGGAGCTCAGCAACCACTTTGCACCATGAGGCAGCACTGAGCACGGTAGGGCAGCC
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FIGURE 142

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VEGTQVTMTCCQSSLCNVPPWQSSRVQDPTGKGAGGPRGSSETVGAALLLNLLAGLGAMG
ARRP
```

Important features of the protein:

Signal peptide:

1-20

Transmembrane domain:

160-180

N-glycosylation site.

78-81

82-85

N-myristoylation site.

86-91

96-101

101-106

123-128

155-160

159-164

177-182

Ly-6 / u-PAR domain proteins

7-26

61-80

124-137

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(74) Agents: BARNES, Elizabeth et al.; MS49 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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[Continued on next page]

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(54) Title: TRANSGENIC MODELS FOR DIFFERENT GENES AND THEIR USE FOR GENE CHARACTERIZATION

(57) Abstract: The present invention relates to transgenic animals, as well as compositions and methods relating to the characterization of gene function. Specifically, the present invention provides transgenic mice comprising disruptions in PRO69122, PRO204, PRO214, PRO222, PRO234, PRO265, PRO309, PRO332, PRO342, PRO356, PRO540, PRO618, PRO944, PRO994, PRO1079, PRO1110, PRO1122, PRO1138, PRO1190, PRO1272, PRO1286, PRO1295, PRO1309, PRO1316, PRO1383, PRO1384, PRO1431, PRO1434, PRO1475, PRO1481, PRO1568, PRO1573, PRO1599, PRO1604, PRO1605, PRO1693, PRO1753, PRO1755, PRO1777, PRO1788, PRO1864, PRO1925, PRO1926, PRO3566, PRO4330, PRO4423, PRO36935, PRO4977, PRO4979, PRO4980, PRO4981, PRO5801, PRO5995, PRO6001, PRO6095, PRO6182, PRO7170, PRO7171, PRO7436, PRO9912, PRO9917, PRO37337, PRO37496, PRO19646, PRO21718, PRO19820, PRO21201, PRO20026, PRO20110, PRO23203 or PRO35250 genes. Such in vivo studies and characterizations may provide valuable identification and discovery of therapeutics and/or treatments useful in the prevention, amelioration or correction of diseases or dysfunctions associated with gene disruptions such as neurological disorders; cardiovascular, endothelial or angiogenic disorders; eye abnormalities; immunological disorders; oncological disorders; bone metabolic abnormalities or disorders; lipid metabolic disorders; or developmental abnormalities.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:
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PCT/US2006/019651

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/27088 A2 (MOUNT SINAI HOSPITAL CORP [CA]; DONOVIEL DORIT [CA]; BERNSTEIN ALAN [C]) 3 June 1999 (1999-06-03) page 30; figures 1,5	1-149
Y	EP 1 038 957 A1 (OTSUKA PHARMA CO LTD [JP]) 27 September 2000 (2000-09-27) paragraph [0049] - paragraph [0051]; sequences 1; 2	1-149
Y	US 2003/186303 A1 (WANG YIXIN [US]) 2 October 2003 (2003-10-02) claim 1; table 1; sequence 23	1-149
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

15 January 2007

Date of mailing of the international search report

31/05/2007

Name and mailing address of the ISA/

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/019651

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	THOMAS K R ET AL: "SITE-DIRECTED MUTAGENESIS BY GENE TARGETING IN MOUSE EMBRYO-DERIVED STEM CELLS" CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 51, 6 November 1987 (1987-11-06), pages 503-512, XP002052221 ISSN: 0092-8674 the whole document -----	149
Y	BIUNNO I ET AL: "SEL1L, THE HUMAN HOMOLOG OF C. ELEGANS SEL-1: REFINED PHYSICAL MAPPING, GENE STRUCTURE AND IDENTIFICATION OF POLYMORPHIC MARKERS" HUMAN GENETICS, BERLIN, DE, vol. 106, no. 2, February 2000 (2000-02), pages 227-235, XP000997779 ISSN: 0340-6717 figures 1,2 -----	1-149
Y	& DATABASE EMBL [Online] 2 February 2000 (2000-02-02), "Homo sapiens SEL1L (SEL1L) mRNA, complete cds." retrieved from EBI accession no. EM_HUM:AF052059 Database accession no. AF052059 -----	1-149

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

Present claims 46, 47, 52, 53, 63, 64, 86, 87, 90, 92, 93, 98, 99, 102, 139, 140, 143-149 relate to an agent which has a given desired property or effect, namely that it is an agonist or an antagonist of PR069122 and to uses thereof. However, the description does not provide support and disclosure in the sense of Article 6 and 5 PCT for any such agent having the said property or effect and there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claim (PCT Guidelines 9.19 and 9.20).

The search of said claims was consequently restricted to antibodies or antisense sequences for PR069122 and uses thereof.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/019651

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

1-149 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: 1-149 (all partially)

Methods for identifying a phenotype associated with a disruption of a gene encoding a PR069122 polypeptide represented by sequences ID nos 1 (nt sequence) and 2 (aa sequence), methods for identifying agents modulating said phenotype and so identified agents, cells derived from the transgenic animal comprising said disruption, methods for identifying agents that modulate the expression of PR069122 and so identified agents, methods of treatment of conditions associated with a disruption of PR069122.

Inventions 2-71: claims 1-149 (all partially)

Methods for identifying a phenotype associated with a disruption of a gene encoding the list of polypeptides listed in claim 1 represented by sequences ID nos 3-142 (nt and aa sequences), methods for identifying agents modulating said phenotype and so identified agents, cells derived from the transgenic animal comprising said disruption, methods for identifying agents that modulate the expression of said polypeptides and so identified agents, methods of treatment of conditions associated with a disruption of the genes encoding said polypeptides.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2006/019651

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☒ furnished subsequently to this Authority for the purpose of search
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/019651

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9927088	A2	03-06-1999 CA 2309677 A1	03-06-1999
EP 1038957	A1	27-09-2000 CA 2311646 A1	10-06-1999
		CN 1280617 A	17-01-2001
		WO 9928457 A1	10-06-1999
		JP 11215987 A	10-08-1999
		US 6822083 B1	23-11-2004
US 2003186303	A1	02-10-2003 NONE	